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Review Article

Congenital and acquired toxoplasmosis: diversity and role of antibodies in different compartments of the host

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SUMMARY

The apicomplexan parasite Toxoplasma gondii *is remarkable in several aspects, since it is a protozoan that infects most nucleated cells in many warm-blooded animals, worldwide. Although the cellular immune response against* T. gondii *is critical for infection control, antibodies may either enhance or block protective mechanisms, and even mediate immunological damage, directly or indirectly. Since cytokines regulate the class/subclass switch, antibodies may also be the biomarkers of protective or pathological cellular immune events. There is a scientific and clinical interest in the presence of natural and autoreactive antibodies, as well as in the 'chronic' immunoglobulin M (IgM) response and the post-treatment 'rebound'. Another interesting aspect is compartmentalization; certain immunoglobulins may uniquely be found in specific host fluids. Local synthesis has been demonstrated, but antibodies may also traverse several cell layers, like the blood–brain and haemato-ocular barriers, and the placenta. In some instances, Fc receptors (FcRs) facilitate transport and may even have a concentrator effect, which can be related to resistance or pathology. These aspects of the humoral response against* T. gondii *are reviewed in the present paper.*

Keywords *antibodies*, *compartments*, *complement*, *cytokine regulation*, Toxoplasma gondii, *toxoplasmosis*

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INTRODUCTION

Toxoplasma gondii is an obligate intracellular protozoan that infects a great variety of warm-blooded hosts, including humans, and has a worldwide distribution (1). This infection can cause severe life-threatening disease in immunocompromised patients and in newborns with congenital toxoplasmosis (1,2). Tissue pathology associated with *T. gondii* infection results from parasite-induced destruction of host cells, and this is related to the virulence of the infecting strains. Virulence is categorized as: (i) type I, the most virulent; (ii) type II, more common and less pathogenic; and (iii) type III, uncommon and phenotypically variable. Recombinant and atypical strains have also been reported (3,4). Approximately 80% of individuals with toxoplasmosis are asymptomatic, partially due to effective innate responses (1,5–7). During the early phase of infection, neutrophils, macrophages and natural killer (NK) cells comprise the main host response against *T. gondii* through phagocytosis, cellular cytotoxicity and production of IFN-γ by naïve NKs (Figure 1). Macrophages and dendritic cells (DCs) present antigens to $CD4^+$ and $CD8^+$ thymocytes, inducing a Th1 phenotype by IL-12 secretion. IFN-γ activates effector cells enhancing phagocytosis, NK-ADCC and $CD8^+$ MHC-mediated cytotoxicity. TNF-α and nitric oxide (NO^-) are produced by activated macrophages, further increasing parasite destruction. If a primo-infection initially occurs in a Th2-cytokine environment (IL-4), *T. gondii* replication is not blocked, and clinical problems secondary to parasite-induced tissue destruction arise. Key ILs against parasite replication are: IL-12, IFN-γ and TNF-α. After parasite control, IL-10 and TGF-β, produced by Th3, regulatory T or DCs modulate the strong pro-inflammatory Th1 response which, uncontrolled, may even kill the host. This general model has been derived from evidence acquired in experimental models (8,9). The kinetics of the response is

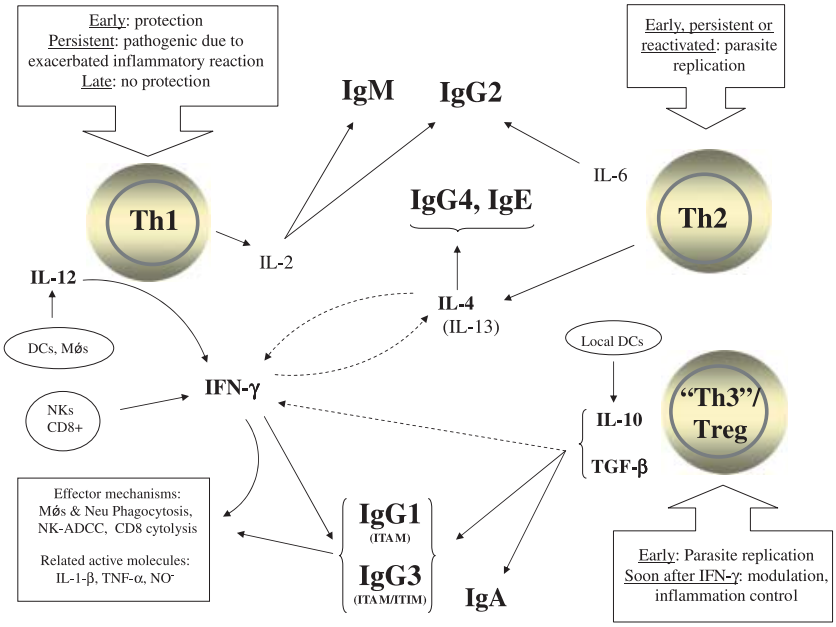

Figure 1 Schematic representation of main immunological phenomena during toxoplasmosis and of antibody class/subclass switches in humans. ADCC, antibody-dependent cell cytotoxicity; DCs, dendritic cells; ITAM, stimulatory intracellular signal in macrophages and NKs; ITIM, regulatory intracellular signal in B cells; Møs, macrophages; Neu, neutrophils; NK, natural killer cells. Continuous and dashed arrows represent positive and negative regulation, respectively.

probably different in humans, as suggested by the antibody class and subclass emergence after infection (see below).

Even though the cellular branch of the immune response is critical for parasite control, antibodies are also important; thus, several aspects of the humoral response against *T. gondii* are reviewed and discussed herein. To facilitate this, information on cytokine regulation, specific cell receptors and effector functions of immunoglobulins is summarized in Tables 1 and 2 (10–22).

ANTIBODY ISOTYPE KINETICS, NATURAL ANTIBODIES AND REBOUNDS

After 3–10 days of *T. gondii* infection immunoglobulin M (IgM) antibodies appear in serum, regardless of parasite strain and host species, sex or age. This is congruent with a positive regulation by the early T and B cell growth factor, IL-2 (Table 1, Figure 1). IgM antibodies were first thought to be present exclusively during the acute phase, but they have repeatedly been found months or even years later, especially in pregnant women and patients with acquired toxoplasmosis involving lymphadenopathy (23,24). Sibalic *et al*. studied four cases and found that specific IgM antibodies reappeared at the time of congenital toxoplasmosis reactivation later in life, or possibly persisted for an extraordinarily long period of time (25). In fact, the phenomenon is more general and the presence of these long-lasting antibodies is intriguing. While a continuous microreactivation of cysts cannot be excluded, other phenomena, like the generation of cross reactive hetero- or autoantibodies, may also be operating. IgM is followed by IgA, which persists for 6–7 months, although it varies considerably in degree and duration both in adults and in congenitally infected newborns (24,26,27). The IgA response regularly appears before any IgG subclass, but this class is up-regulated by IL-10 and TGF-β (Th3/Treg cytokines) (12). Likewise, IgE antibodies are detectable during the acute phase although they are induced by IL-4 (Table 1). They have been found in up to 86% of adults who seroconvert and do not last for more than 4 months, although they persist in patients with severe toxoplasmosis and lymphadenopathy (27–29). IgE antibodies are produced by few congenitally infected newborns and are markers of poor adherence to treatment or rebound (27–29). Thus, the model of a Th1-phenotype response during an early phase, followed by a Th2/Th3/Treg-response would not seem to be supported in human infection. Nevertheless, it has been shown that the cytokines and antibodies produced at a given moment may vary considerably in terms of type and intensity in different body sites. For example, some parts of the intestine of experimentally infected pigs expressed high levels of IL-10 mRNA at the same time as other body sites presented a Th1-phenotype response (9). Likewise, local DCs stimulate the production of IgA by secreting IL-10 concomitantly with IL-12 synthesis by peripheral DCs, which stimulate IFN-γ synthesis (Figure 1) (30). These locally stimulated antibodies could reach the general circulation and be detectable before the IFN-γ-induced IgG isotypes are produced systemically.

Mice do not develop IgE antibodies in response to infection or immunization with *T. gondii* antigens (31). Thus, the murine model for isotype regulation has been based on the IgG subclasses that follow IgM and IgA activation. During

Table 1 General features of immunoglobulin classes and subclasses

Characteristics	Human class/subclass									
	IgG	IgG1	IgG2	IgG3	IgG4	IgA	IgA1	IgA2	IgM	IgE
Equivalent in mice	IgG	IgG2a	IgG3	IgG2b	IgG1	IgA	–	–	IgM	IgE
Half life (days)		21–23	20–23	7–16	21–23		6	6	5	2
Interleukin regulation										
Switch inducers		IFN-γ, IL-2	IL-2	IFN- γ	IL-4, IL-13	TGF-β			IL-2	IL-4, IL-13
Switch enhancers		IL-10, IL-21	IL-6	IL-10, IL-21	IL-13, IL-6					IL-13
Switch inhibitors		IL-4			IFN-γ					IL-21, IFN- γ
Levels in:										
Normal adult serum (mg/mL)	10·0–15·0	5·0–12·0	2·0–6·0	0·5–1·0	0·2–1·0	0·2–2·0	0·5–2·0	0·0–0·2	0·5–1·5	0–0·002
(% total)		(60–72)	(19–31)	(5–8)	(0·7–1·0)					
Placental transfer		++	+	++	++		–	–	–	–
Term cord blood serum (mg/mL)	13–19	2–9	1–5	0·1–1·5	< 0·1–0·8				0·05–0·15	
Colostrum (mg/mL)		0·037	0·035	< 0·003	0·005		8·8–13·0	13·3–17·5		
Milk (mg/mL)		0·025	0·020	< 0·002	0·004		0·29–0·43	0·21–0·33		
% of total IgG in colostrum/milk		47	44	< 4	6					
Cerebrospinal fluid (mg/mL)	0·025–0·075									
Saliva (mg/mL)	> 0·015	0·010	0·019	< 0·002	0·001	0·02			0·002	
% of total IgG in saliva		27·9	53·7	< 4·6	3·7					
Tears (mg/mL)	< 0·001–0·007					0·19–0·31			< 0·001–0·006	

Table 2 Effector mechanisms of the human immunoglobulin classes and subclasses

Binding to Fc receptors	Affinity constant (M); signal transduction	Expressing cells	Function	Human class/subclass								
				IgG1	IgG2	IgG3	IgG4	IgA	IgA1	IgA2	IgM	IgE
FcR-lo	Low	Neu, Mφs, Eos	Phagocytosis?	++++		++++						
FcγR-I (CD64)	High (~10^{-9}) ITAM	Mon, Mφs, Neu, Eos; MCs	Phagocytosis	+++	–	++	+					
FcγR-lla/c (CD32)	Low (> 10^{-7}) ITAM	Mon, Mφs, Neu, Plat; Lang	Phagocytosis; cell activation (inefficient)	+++	+++	++++	+					
FcγR-IIb (CD32)	Low (> 10^{-7}) ITIM	B cells	Feedback inhibition	+++	+	++++	++					
FcγR-IIIa (CD16)	Low (> 10^{-6}) ITAM	Mon, Mφs, NKs, T cells	Phagocytosis; ADCC	++++	+	++++	+					
FcγR-IIIb (CD16)	Low (> 10^{-6}) GPI-linked protein	Neu, Eos	Phagocytosis (inefficient)	++++	+	++++	+					
FcεR-I (binds monomeric IgE)	High (~10^{-10}) ITAM	Mon, Mφs, Bas, Lang, Eos	Cell activation and degranulation									+
FcεR-II (CD23); C-Type lectin	Low (> 10^{-7})	Mon, Mφs, B, T, DCs, Plat, Eos, Lang, Epit	Unknown									+
FcαR-I (CD89)	Low (> 10^{-6}) ITAM	Mon; Mφs, Neu, Eos, Kup, DC	Cell activation?					+				
Fcα/μR	Unknown	Unknown	Unknown					+			+	
FcRn	Low (> 10^{-7})	Trophoblasts and foetal endothelial cells	Placental passive transfer									
Classical complement fixation				++	+	++	–		–	–	+	–
Alternative complement fixation				–	–	–	–		+	+	–	+/–

FcR, Fc receptor; ITAM, positive transduction signal; ITIM, negative transduction signal; Mon, monocytes; Mφs, macrophages; Neu, neutrophils; NKs, natural killer cells; Plat: platelets; Eos, eosinophils; Bas, basophils; MCs, mastcells; Lang, Langerhans cells; DCs, dendritic cells; Epit, epithelial cells; Kup, Kupfer cells; ADCC, antibody-dependent cell cytotoxicity.

the acute phase, IgG2a and IgG2b, mainly induced by IFN-γ, arise while IgG1, up-regulated by IL-4 and IL-13, is considered to be a marker of the chronic phase (Table 1) (8,31). The relation between the cytokine profile and the IgG subclass induced is more complex in humans (Figure 1). It has been shown that IgG1 and IgG3 are induced by IFN-γ, and enhanced by IL-10 and TGF-β. IgG2 is switched by IL-2 and augmented by IL-6 (Th2, pro-inflammatory), while IgG4 is induced by IL-4 and IL-13. Several studies on the kinetics of the IgG subclasses appearing following infection in humans have shown that IgG1 is activated earliest and is dominant in serum, while the kinetic patterns observed for IgG2, IgG3 and IgG4 are quite variable. An intriguing aspect may be the late appearance of IgG2 reported in one of these studies, since it is normally stimulated by IL-2, a cytokine produced very soon after infection in the murine models (32,33).

Potasman *et al*. described the presence of natural IgG and IgM antibodies in the serum of noninfected individuals, with a heterogeneous pattern for IgG and a more homogenous one for IgM (34). Remarkably, and unlike mice, human CD4+ αβ cells from nonexposed individuals can be primed *in vitro* to produce IFN-γ, and to express both CD45RA and CD45RO in response to *T. gondii* antigens (35). The presence of IgA antibodies in tears of 51 out of 62 healthy individuals, in a population with a 25% seroprevalence of *Toxoplasma* IgG, was separately reported. Although they could be natural antibodies, the authors suggested that they may instead reflect the existence of resistant individuals, rapid responders who reject infection, since tears are more related to the mucosal than to the ocular or systemic response (36). Cross reactions with nonparasite molecules (including host antigens) may alternatively explain the presence of natural antibodies.

Sudden increases in serum antibody titres, or rebounds, have been observed especially in congenitally infected infants after treatment (37–40). A reactivation of the acute phase of the parasite might induce rebound. In this regard, specific antibody secreting cells in the peripheral blood of some congenital and HIV-1-infected patients with *T. gondii* encephalitis have been observed (38,41). This phenomenon could also be due to reinfection, and the finding of IgM antibodies in some cases after treatment suspension would support this notion (39). Release of antigens without reactivation could also explain antibody rebound, but bradyzoites are poorly antigenic for the human host (see below), and no correlation with clinical recrudescence has been documented. It is also probable that the antibody secreting cells are the result of polyclonal B-cell stimulation, due to renewed haematopoiesis after suspension of pyrimethamine treatment. In this case, other antibodies might occur and increase concomitantly with anti-*T. gondii* titres. IgE antibodies appear in many cases during rebound, probably due to a switch to a Th2-profile (40).

ANTIGEN TARGETS

Toxoplasma gondii antigens have been of enormous interest for different reasons, including aspects of diagnosis and follow-up, vaccine development and basic research. They have been classified into families according to their cellular location (i.e. SAG for surface antigens; MIC for micronema; GRA for dense granule; and ROP for rhoptry). Most components are important for invasion, parasitophorous vacuole formation, immune evasion or exit from the host cell after replication. Some antigens are known immunodominant molecules, like SAG1 (p30), SAG2 (p22) and a low molecular weight band (42–44). Nonetheless, the humoral response is very heterogeneous among individuals and against different stages of the parasite. The existence of multiple epitopes has been ascertained by microarrays (45). IgG antibodies, especially IgG1, react to high numbers of whole parasite or excretion/secretion antigens, which range in molecular weight from 4 to > 115 kDa (42–44,46).

Published reviews of some of the earlier discovered stage-specific antigens have clarified their characteristics and role in *Toxoplasma* infection (47,48) Briefly, bradyzoites express few unique antigens, like SAG4, but share some SAG2 family components with tachyzoites, while SAG1 and SAG3 are tachyzoites-specific. Some isoenzymes and heat shock proteins (HSP) are also differentially expressed. Many antigens of the tachyzoite are recognized early, although the antibodies reacting with them may last for years, while the bradyzoite is barely antigenic in humans. It is therefore difficult to differentiate an acute from a chronic phase of infection by the antigenic pattern recognized.

Of special interest are 'neoantibodies', present in the serum of infected newborns and absent in their paired mother's serum, which are defined as Western blot bands uniquely or more strongly recognized by the newborn (49–52). The positive predictive value of these newborn-related bands seems lower than 80%, so their differential capacity is limited (51). An explanation of their presence is placental transport of individual antigens, either alone or in the form of immune complexes (as has been documented for other antigens), which would make them available for active antibody production by the foetus, without active passage of the parasite through the placenta (22).

COMPARTMENTALIZATION OF THE ANTIBODY RESPONSE

Mucosas and secretions

With the exception of the congenital cases, natural infection occurs through the oral route, and an early local response occurs. Several studies report on the presence of mucosal

antibodies measured in saliva, intestinal fluids, milk and tears, and have clarified their nature and local synthesis. Using agglutination assays, Hajeer *et al*. identified IgG, IgM and IgA anti-*T. gondii* antibodies in the saliva of acutely infected individuals (53). Then, it was shown that salivary IgA, unlike IgG, reflects its serum level (54). More recently, specific IgG was found in the saliva of 64% and 98% of HIV/AIDS patients with toxoplasmic encephalitis (TE) and healthy donors, by ELISA and Western blot, respectively. In the first group, IgM antibodies were also found in 81% of saliva samples (55,56). IgA antibodies were 18 times more frequent in tears of patients with uveitis than in those without it; moreover, five cases who had secretory IgA in tears were serum IgA-negative, suggesting local production (57). In experimental rodent models, oral infection induces early IgA antibodies in intestinal secretions, differing in kinetics from those of IgG, IgA and IgM in milk and serum (58,59). IgA is up-regulated by TGF-β and IL-10, and mesenteric lymph node DCs seem to play an important role in its local production (30,60).

The central nervous system and the eye

TE is one of the more serious consequences of *T. gondii* infection, mainly due to parasite reactivation following immunosuppressive drug therapy or HIV/AIDS. Contradictory results have been reported in relation to brain cavity production of antibodies vs. transfer across the blood–brain barrier. Potasman *et al*. reported local production in TE/AIDS patients with systemic low levels compared to those in the cerebrospinal fluid (CSF) (61). Intrathecal IgG antibody synthesis was also detected in 6 out of 11 cases with TE (62). Conversely, oligoclonal bands against *T. gondii* antigens were found by Western blot in the CSF of some TE/AIDS patients, but these antibodies came from the systemic level (63). SAG1, anti-SAG1 antibodies and immune complexes were found within the CSF of patients with toxoplasmosis, with or without concomitant HIV infection (64). More recently, the presence of specific IgA, IgM and IgG antibodies was found in the CSF of patients with TE, although it was not established if they were locally produced or traversed the blood–brain barrier (65). Current evidence indicates that antibodies can be produced either within the brain or migrate into it from elsewhere in the body. Less clear is the role of antibodies in the brain–parasite interface, although experiments with μMT mice (which cannot produce immunoglobulins) showed that antibodies are important to control tachyzoite replication at the central nervous system level (66).

Intraocular IgM, IgA and IgG antibodies were demonstrated long ago and, in some studies, they were shown to be synthesized within the eye (67–69). IgA was found to be related to the evolution time of disease, interestingly being present less frequently in acute cases (70). Antibody transfer across the blood–eye barrier is uncommon. Negative intraocular results have been reported from *T. gondii*-seropositive patients without ocular involvement and local synthesis, and slow transfer of IgA and IgG antibodies have been shown in cases with ophthalmic problems (71,72).

The presence of IgG antibodies in intraocular and CSFs was found in a model of feline immunodeficiency virus/*T. gondii* co-infection in cats, although no correlation with the local lesion was observed (73). In the same model, systemic immunization with soluble parasite antigens induced local antibody production in the intraocular fluid and the CSF, although it was not related to either eye or brain inflammation (74). The kinetics and role of different classes/subclasses of antibodies in parasite control or pathogenesis in human and animal neuro-ophthalmo toxoplasmosis remain to be elucidated.

Transfer across the placenta and foetal antibody synthesis

Congenital toxoplasmosis was the prime medical problem caused by *T. gondii* before the apparition of the HIV pandemic. Thus, the search for specific foetal markers of infection has long been of interest. The hepatic tissue is able to produce IgM and IgG at 8–9 weeks of gestation, while IgA may be produced some weeks later (75). During the first trimester, vertical transmission is uncommon, but by the end of gestation it approaches 80%, when, paradoxically, the defence mechanisms of the foetus and the transferred maternal components, among them specific antibodies, are maximal (76). IgM, IgA and IgE do not cross the placenta (Tables 1 and 2); thus, their presence in foetal and newborn blood is considered diagnostic of congenital infection. An interesting study showed that *T. gondii*-specific IgA was found in the amniotic fluid of six out of seven cases in which the parasite was isolated, but also in 45% of 'noninfected' cases (77). The fluid samples were from women who seroconverted; thus, the 'negative' foetuses could have been infected, but not detected, due to the low sensitivity of the parasite isolation technique used. An alternative explanation is that FcRn receptors of the syncytiotrophoblast and foetal vascular endothelial cells transported IgG-complexed antigens, which in turn might have stimulated foetal IgA synthesis (22). Regarding the timing of anti-*T. gondii* antibody production, it is worth mentioning that Decoster *et al*. suggested that neonatal IgA and IgM could be present only in infections acquired during the third trimester (78). Wallon *et al*. later found that this was not exact, although the sensitivity of tests in newborns increased at later trimesters following the mother's seroconversion: 40%, 42% and 70% for IgM, and 0%, 60% and 64% for IgA (79). Recently, a similar phenomenon in relation to IgM was reported, but a

constant frequency around 50% along pregnancy was observed for IgA (80). The lack of IgM in 60% of foetuses infected during the first or second trimester could be due to a short lasting primary response, disappearing at the time of delivery, or an inability of some embryos to produce it (although this isotype develops very early during intrauterine life). IgA is the latest class to appear during ontogeny, and reaches maturity by 8–12 years of age; thus, it is not surprising that a first trimester infection does not induce its synthesis by the embryo (or does it in few cases) (75).

The existence of an active and controlled transport of all four subclasses of IgG across the human placenta has been extensively demonstrated, with a close to linear relationship between gestational age and placental transfer. This is mediated by the exclusive syncytiotrophoblast/foetal endothelium FcRn (Table 2). We have recently found evidence of placental transfer of IgG1 and, in some cases IgG2 and IgG4, in seropositive mothers who delivered noninfected newborns (Cañedo *et al*. submitted). That is why IgG antibodies are not used as markers of congenital infection (22).

PROTECTIVE AND PATHOLOGICAL ROLES OF ANTIBODIES

B-cell deficient animal models, as well as other *in vivo* and *in vitro* assays have shown that antibodies form part of the protective host response mechanisms against *T. gondii* infection (66,81–83). In B-cell deficient mice from both C57BL6 (susceptible) and Balb/c (resistant) strains, passive transfer of antibodies inhibited parasite proliferation in the peritoneum (66). Likewise, passive transfer of immune serum prolonged survival of CD4+ knockout mice with intact CD8+ and IFN-γ responses, or induced a significant degree of protection towards the virulent RH strain of *T. gondii* in highly susceptible nu/nμ rats (81,82). Also, it has been shown that mice deficient in CD8+ CD4+ T cells or B cells exhibit diminished vaccine-induced resistance and increased ocular parasite burden after challenge (83).

Mechanisms underlying antibody protection include neutralization and inhibition of parasite cell invasion. IgM, IgA and IgG antibodies of humans, rabbits and mice, respectively, specific for whole antigen, excretion/secretion products or SAG1, can block host cell entry at both the systemic and mucosal levels (58–60,84).

IgM, as well as human IgG1 and IgG3 (murine IgG2a and IgG2b), are strong activators of the classical pathway of complement and promote inflammation. Also, IgA of both subclasses may activate the alternative pathway (Table 2). Complement activation and parasite killing has been shown for several isotypes, and some indirect results in animal models suggest this mechanism may be operating for other isotypes (85,86).

Human IgG1 and IgG3 are similar to mouse IgG2a regarding ability to bind to IFN-γ stimulated macrophages and neutrophils through Fc-γ receptors, opsonizing them (Table 2). Nonadherent and adherent human monocytes are equally infected by *T. gondii* independently of opsonization with SAG1 specific rabbit IgG (which binds to Fc-γRI of humans), but adherent cells with intact FcRI and II expression present half the parasite burdens of those with down-regulated Fc receptors (FcRs) (87). IFN-γ activated NK cells also display FcγRIII, which binds these antibody subclasses, and kills tachyzoites through ADCC (Table 2) (19). Mice deficient in FcγRI/III/ε or FcγRII resisted infection after transference of immune serum. Although it was suggested that neutralization was mainly responsible for protection, the FcR effect could not be excluded since single knockouts were used, and thus, in the absence of one FcR, the other(s) could be functioning (87). The partially protective role of IgE antibodies (plus IgG and complement) has been observed in passive transfer experiments in nu/nμ rats. The role of eosinophils and platelets through the FcεR has also been proposed (88). This proposal advances the notion that IgE plays a protective role, contrary to previous reports suggesting its association with pathogenesis (Figure 1, see below).

In many experimental and natural infections antibodies are positively associated with clinical or parasitological findings. Classical examples are IgE antibodies in humans (probably also IgG4) and IgG1 in mice. These isotypes are linked to a Th2 profile and they can activate pathological pathways or block protective functions. For example, IgE mediates eosinophil and mast cell reactions which may generate deleterious systemic problems and local inflammation, while human IgG4 inhibits binding of C1q to IgG1 (Table 2) (89). IgE antibodies are associated with the majority of unresolved lymphadenopathy cases of acquired toxoplasmosis (28,29). IgG2 has been found in human serum. Its switch is promoted by IL-2 but is enhanced by IL-6, a pro-inflammatory cytokine. It has poor complement-fixing and opsonizing activities (Tables 1 and 2). Data from our laboratory showed an isotype specific response in mother/newborn pairs, associated with clinical outcome. We found a high proportion of infected babies positive for IgG2 or IgG4 by ELISA, related to congenital infection or clinical abnormalities (Cañedo *et al*. submitted).

Th1 related isotypes may also be associated with clinical problems, due to a nonmodulated Th1 profile, which in fact can kill the host (90). In humans with ocular acquired toxoplasmosis a mononuclear inflammation is probably the cause of the disease (91). Complement-fixing and opsonizing immunoglobulins could be linked to an exacerbated inflammation with production of anaphylatoxins, TNF-α and NO^{-}. Alternatively, retinal damage can be caused by autoantibodies against local host antigens, found in a higher

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proportion of patients with toxoplasmic chorioretinitis than in patients with other ocular diseases or healthy controls (92). Antibodies could add damage to the retina by fixing complement or opsonizing macrophages. In this regard, it was shown that autoreactive cellular or humoral responses prompted inflammatory reactions in the eyes of experimentally infected mice (93). Anti-*T. gondii* HSP70 antibodies were observed in the sera of Balb/c and C57BL/6 mice after oral infection with *T. gondii* cysts, but autoreactive IgG was detected at higher levels and for longer periods in susceptible than in resistant mice (94). A main profile of B1 cell autoantibody production was observed for the B6 (susceptible) strain, with increasing avidity along the course of infection (95).

CONCLUDING REMARKS

A very complex phenomenon occurs when a host is infected by *T. gondii*, and antibodies are important molecules in control or pathogenesis. Their role depends on recognition of antigen targets, compartment, appearance and persistence time, and effector functions. Since they are regulated by cytokines, they may be markers of co-occurring cellular and molecular events, and are invaluable in diagnosis support. In many cases, their presence, rebound or persistence is intriguing. Scientific research to date has been able to elucidate the numerous roles of these molecules in the process of toxoplasmosis infection and disease, but many still remain to be discovered.

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