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Review Article

Toxoplasmosis: Role of Cytokines in Disease Modulation & Tissue Pathology

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Abstract

Toxoplasmosis caused by *Toxoplasma gondii* parasite has a world - wide distribution effecting one third of the world population. A number of parasite and host factors determine the outcome of prevalence, disease severity and tissue damage ranging from asymptomatic self - limiting infection in health adults to serious destructive inflammatory consequences in congenitally infected infants and in individuals with a weakened immune system.

There is strong experimental evidence that the cytokines play a major role in the pathogenesis of *Toxoplasma gondii* and manipulation of these cytokines can put forth a beneficial or damaging effect on the host and thus modulate the disease pathology. The importance of interferon gamma (IFN-γ) was clearly demonstrated when the neutralization of interleukin (IL) IL-12 and of IFN-γ using anti-IFN-γ & anti-IL-12 monoclonal antibodies (MAb) resulted in reactivation and loss of control on the parasite's multiplication leading to disease. Cytokine IL-27 was deemed as an endogenous suppresser on IL-17, the inflammatory cytokine that is capable of enhancing the inflammatory response in the brain. Although *Toxoplasma* is an intracellular pathogen thereby requiring a cell mediated immune response from the host, the cytokine IL-10 protects the infected mice from an exaggerated cellular immune response by inhibiting the production of pro - inflammatory cytokines: IL-12, IFN-γ, and TNF-β. Following Toxoplasma infection the host triggers a sequential balanced cytokine response to limit the infection and the disease pathology. However, cytokines can sometimes exert a negative effect on the host and augment the disease leading to severe irreversible tissue damage.

ABBREVIATIONS

T. gondii: *Toxoplasma Gondii;* IFN- γ: Interferon Gamma; TNF: Tumour Necrosis Factor

INTRODUCTION

Toxoplasma gondii belonging to the phylum *Apicomplexa*, is an obligate intracellular parasite that can invade and replicate in almost all nucleated cells of virtually all warm blooded animals, including humans. It has a world - wide geographical distribution affecting one third of the world population. Humans may acquire the infection by ingestion of oocysts or congenitally by transplacental transmission from the infected mother [1]. The prevalence of *T. gondii* -specific antibodies in adults increases with age but differs widely due to temperature and humidity variation, as well as different population and ethnic groups within the same country [2-4]. In the USA and UK, approximately 16-40% of the population is infected, whereas in Central America and Continental Europe 50-80% people are infected [5].

A number of parasite and host factors determine the outcome of infection. The most important factors appear to be the mode of infection, parasite strain and host immunogenic characteristics [6,7]. The majority of infected immune competent healthy adults are asymptomatic however; it may cause serious destructive inflammatory consequences in congenitally infected infants [8] and in individuals with a weakened immune system [9,10]. During the early stages of pregnancy, the presence of fetal antigens in the circulation, low levels of progesterone and 17-β estradial may alter the immune responses of the mother thus increasing the susceptibility to active infection which may cause apoptosis of placental cells and fetal resorption inducing the congenital malformations in the growing fetus [11,12].

Though *T. gondii* parasite has been shown to have low genetic diversity and a clonal population but there is a growing evidence that the three genetically different type-I, type-II and type-III parasite strains may determine the outcome of infection and tissue pathology in the host. Type I strains are shown to be highly virulent and cause rapid death in mice, whereas the outcome of

infections with type II and III strains depends on the challenge dose and genotype of the host [13-15].

Figure (1) presents geographic association between parasite strains ("Types" or "Haplogroups" I through XVII), prevalence of human infection, severity of human infection and mouse virulence.

Within the *Toxoplasma* parasite life cycle, two stages have been observed; the sexual stage which is rather distinct and highly specific as it occurs only within the gut epithelial cells of feline species. On the contrary, asexual stage has a large repertoire capable of infecting several vertebrate intermediate species including humans. In the intermediate hosts, the oocysts (bradyzoites) change from their slow - growing phase into tachyzoites, the rapid replication phase infecting almost any nucleated cell they encounter, multiplying intracellular leading eventually to host cell lysis. Following infection, an immune competent individual develops immunity to the tachyzoites changing the parasite to the slow multiplying stage (bradyzoites). The bradyzoites stage ensures the survival of the parasite within the cysts in the muscles and central nervous system by shielding it from the host's immune surveillance. However, in immune compromised hosts, the parasite rapidly changes to the rapidly replicating stage causing an active multi-organ infection [16].

Toxoplasma parasite-host cell interaction

Toxoplasma host cell invasion is an active, parasite - driven process accompanied by release of a number of polymorphic parasite proteins and factors that interact with the host cell and thus may alter the host resistance to infection and tissue pathology. These proteins and factors are released from apical secretory organelles. Over the past 15 years it has become increasingly clear that many of these secreted effectors manipulate host immune defense mechanisms and determine differences in parasite virulence (Figure 2) [17,18].

A single mutation in a secreted rhoptry protein (ROP16) determines activation of the immune communication pathway called the "STAT6 signaling pathway" by the *Toxoplasma* strains and thus the host immune response to worm infections.

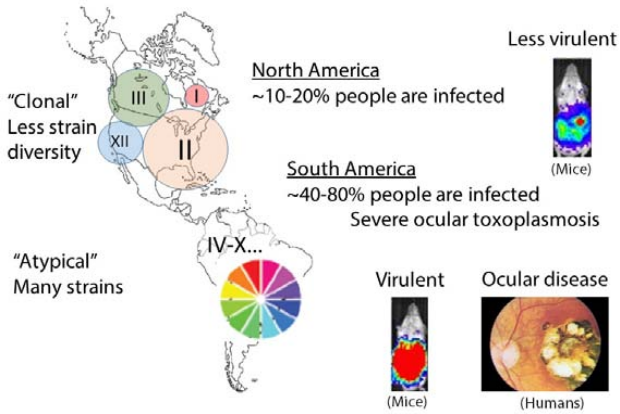

Figure 1 Geographic association between parasite strains.

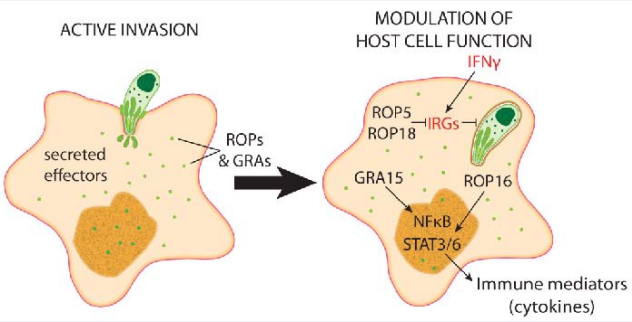

Figure 2 Modulation of host cell function following *T. gondii* parasite infection.

Toxoplasma parasite either turns this pathway on or off depending on the strain type and ROP16 version (allele) it encodes. Different parasite strains encode particular combinations of active and inactive effectors. Thus, a little P53 activation, less MAPK and NF-kB signaling, but strong ERK by one strain could be perfect to establish a chronic infection in one species, but lethal or pathogenic in others - mice or humans (Figure 2) [17,18].

Role of pro-inflammatory cytokines

IFN-γ & TNF: A complex network of cytokines produced by interacting immune cells significantly contribute to immunity against the parasite, pathologic hypersensitivity reactions leading to tissue pathology and the course of infection in the host. Earlier, the studies have documented that the control of Toxoplasma infection in mouse with non - virulent strains is achieved by a vigorous IFN- γ -dependent Th1 pro - inflammatory cytokine response by *Toxoplasma* - specific T cells [19,20]. These cells either produce protective cytokines inducing toxoplasmacidal activity or cytokines that are involved in T - cell proliferation in the infected organs [21]. In fact, there is growing experimental evidence that these two aspects of T - cell function may be differentially regulated in different organs by different strains of *Toxoplasma gondii*. Another important task of IFN-γ is to prevent the reactivation of *Toxoplasma* encephalitis in mice. When produced in excess, pro - inflammatory cytokines may lead to tissue damage and thus, a delicate balance between pro and anti - inflammatory cytokines is necessary for the effective control of the parasite and survival of the host.

The production of IFN-γ also activates macrophages to produce tumor necrosis factor - alpha (TNF-α) which synergizes with IFN-γ to initiate production of the anti - microbial molecule, nitric oxide (NO). IFN-γ also controls other effector mechanisms that fight *T. gondii* infection, including generation of reactive oxygen intermediates (ROI), iron deprivation, tryptophan starvation and activation of the p47 GTPases (Miller *et al*., 2009 thesis). The anti - parasitic activity for the latter is due to the accumulation of certain p47 GTPase family members at *T. gondii* -containing vacuoles and successive disruption of the parasitophorous vacuole membrane (PVM) and the parasite [22]. In murine models of ocular *toxoplasmosis*, treatment with either anti-IFN-γ or anti-TNF-α monoclonal antibodies resulted in a dramatic increase in the inflammatory process, retinal - pigmented epithelial pathology, and chorioretinal scars,

demonstrating that IFN-γ and TNF-α are critical in controlling parasite growth [23].

Role of IL-12 & IL-18

In *T. gondii* infection caused by oral route, IL-12 acts synergistically with IL-18 to produce IFN-γ by NK cells. IFN-γ synergizes with IL-12 to drive the differentiation of Thp to Th1 phenotype, express IL-12 receptor on T cells, and inhibit the antagonist IL-4 to prevent the differentiation of Thp towards Th2 phenotype [24]. Conversely, IL-18 seems to have an opposite role where it was found that IL-18 can incite intestinal necrosis and inflammation and mice deficient in this cytokine displayed better survival, decreased parasite load, and only moderate necrosis of the villi and mucosa [25]. On the other hand, IL-12 seems to have a more beneficial role because IL-12 deficient mice displayed severe pathology, decreased survival (as wild types) and increased parasite burden. Hence, although IL-18 is a potent enhancer of IL-12, its production may mediate intestinal pathology while IL-12 is involved in controlling the parasite. In addition, the role of IL-12 was further demonstrated by in vivo depletion studies documenting the ability of exogenous IL-18 to enhance resistance to *T. gondii* infection with IL-12, IFN- γ and NK cells [25].

Role of TGF-β

Transforming growth factor (TGF-β) is a multi-functional cytokine with anti - inflammatory activities and an important suppressor of macrophages, the production of which is induced after infection with *T. gondii* [26]. TGF-β is secreted by Intraepithelial lymphocytes (IELs), particularly by CD8 αβ and TCR αβ, regulates the inflammatory pathogenic responses elicited by lamina propria lymphocytes (LPLs) by down regulating the transcription of IFN-γ, IL-15, iNOS and TNF-α (pro - inflammatory cytokines) [1]. *T. gondii* can remain dormant in the CNS and the eye. In these sites, TGF-β and IL-10 cooperate together by first TGF-β conditioning antigen - presenting cells (APCs) to release IL-10 which in return will decrease NK- and CD4 Th1 - mediated pro - inflammatory responses suggesting that TGF-β is inefficient without IL-10 in immune - privileged sites in controlling the inflammation [1,27]. It also inhibits the production of IFN-γ by NK cells (Hunter et al., 1995-thesis), thus may down - regulate the effector functions of anti - *Toxoplasma* cellular immunity during acute *toxoplasmosis*. TGF-β is an important suppressor of macrophages [26], the production of which is induced after infection with *T. gondii* [28]. It also inhibits the production of IFN-γ by NK cells, thus may down - regulate the effector functions of anti - *Toxoplasma* cellular immunity during acute *toxoplasmosis*.

Role of Anti-inflammatory cytokines

Although IFN-γ-dependent pro - inflammatory cytokines are essential for resistance to *T. gondii* infection, an over -production of inflammatory cytokines and NO can result in serious tissue damage [13,29,30]. Thus, the host needs to balance the response in order to eliminate the parasite while minimizing tissue damage. Anti - inflammatory signals from the macrophages themselves or surrounding cells down - regulate macrophage activation and result in the production of anti - inflammatory cytokines such as IL-10, TGF-β and interleukin-27 [21].

Role of IL-10

The anti - inflammatory cytokine IL-10 plays an important role in reducing harmful pathological effects of inflammatory responses in *T. gondii* infection. IL-10 is a cytokine produced by DCs, macrophages, B-cells, Th2 cells and T - regulatory cells [31,32]. IL-10-deficient mice showed elevated IL-12 levels and consequently increased IFN-γ and TNF-α responses and intense hepatic inflammation and tissue necrosis [30]. During acute *toxoplasmosis*, IL-10 serves a dual role in the suppression of the host's cellular immune response. First, it inhibits IFN-γ production and the proliferation of T-lymphocytes, thus preventing a potentially protective Th1 immune response. Such T-cell-dependent immune suppression exerted by IL-10 primarily appears to avoid overwhelming inflammation which eventually leads to death. Second, IL-10 may also deactivate macrophages, thus reducing IFN-γ-induced toxoplasmacidal activity and facilitating intracellular parasite survival. Hence, IL-10-induced immune suppression following infection with *T. gondii* is beneficial for both the parasite and the host and favors a stable host - parasite relationship [33,34].

Immunopathology in *toxoplasmosis*

Role of cell-mediated immunity in pathological changes: Although an early cell - mediated immune response is necessary to control *T. gondii* infection, an exacerbated response can also participate in tissue damage along with parasite - induced damage.

Toxoplasma infection rapidly overcomes hosts with impaired T - cell function and diminished ability to produce pro-inflammatory cytokines [35]. In recent years, it has become clear that pro-inflammatory and anti - inflammatory cytokine responses must be tightly regulated for optimal control of infection and that cytokine imbalances resulting from loss of control can play a role in the pathological changes associated with *toxoplasmosis* [24]. Nevertheless, it is difficult to experimentally separate pathological changes caused by parasite replication from more systemic damage caused by parasite-induced cytokines.

Acute infection and pathological changes in tissues: In most immune competent patients, acute *toxoplasmosis* results in post - cervical lymphadenopathy and mild fever [36], which occurs along with the activation of the immune system triggered by *T. gondii* and a simultaneous production of high levels of pro - inflammatory cytokines. In most patients, acute *toxoplasmosis* will progress to the asymptomatic stage within a few weeks of infection.

Intestinal pathology: Based on experimental studies on the production of inflammatory mediators during infection in mice, there is evidence that T-cell-derived cytokines may promote pathological changes during *T. gondii* infection. After peroral infection, the susceptible C57BL/6 mouse strain develops a severe intestinal inflammatory response, leading to severe necrosis of the villi and mucosal cells of the small intestine [37]. It was shown that the tissue damage was not parasite - induced, but caused mainly by the development of a strong pro -inflammatory immune response, characterized by overproduction of pro - inflammatory mediators including IL-12, IL-18, IFN-γ, TNF-α,

and NO ('cytokine storm').The tissue damage was characterized by severe ileal necrosis with complete tissue destruction and intensive infiltration of neutrophilic granulocytes, macrophages, dendritic cells and lymphocytes within the lamina propria [37,38].

The role of cytokine - induced tissue damage was substantiated by the reversal of pathological changes when anti -IFN-γ or anti-CD4 monoclonal antibodies (MAb) were administered. In addition, the two MAb also delayed the death in terminally ill mice. It has also been demonstrated that IFN-γ triggers Fas-dependent apoptosis of Peyer's patch T-cells in perorally infected mice [37-39]. Similarly, the depletion of TNF, another inducer of Fas - dependent apoptosis, delayed the death of acutely infected mice with the highly virulent RH strain [40]. An uncontrolled pro -inflammatory cytokine response and the resulting pathological changes mediated by T-lymphocytes, was also confirmed in IL-10 knockout mice [30]. Granulocytes have also been shown to contribute to the inflammatory pathological changes triggered by *T. gondii* infection [40]. Thus, several experimental studies suggest that *Toxoplasma* - induced inflammatory responses, and specifically $CD4^+$ T-lymphocytes and granulocytes, contribute to the pathological damage associated with acute infection in mice.

Ocular pathology: Recently our group has reported that acute infection with *T. gondii* RH parasites, a mild Th1 pro - inflammatory response in the BALB/c mice with high IFN-γ and TNF-α and, low TGF-β 1 levels during the early stages of infection contributes to an effective cellular immune response leading to lower morbidity, mortality and less ocular tissue damage. However in the MF1 mice, a significantly high TGF-β1 level in the blood as well as in the aqueous humor during the acute intra - ocular toxoplasma infection adversely interferes with an effective cellular immune response leading to an increased mortality and extensive ocular tissue damage with parasite tachyzoites observed in the pigment epithelium layers (Figure 3,4) [14].

Chronic infection and pathological changes in tissues: The appearance of bradyzoites marks the beginning of the chronic phase of infection when parasite replication slows dramatically. Tissue cysts appear to be practically invisible to the host since there is little or no evidence of inflammation or immune cell infiltrates around them [41].

In reactivation of a latent *T. gondii* infection, cysts may occur in a variety of tissues, but the most important clinical site is the central nervous system, where uncontrolled parasite replication may lead to toxoplasmic encephalitis (TE). In the wake of low T-cell counts and declining local IFN-γ levels, bradyzoites revert to tachyzoites, which rapidly proliferate in astrocytes and microglia causing tissue necrosis [42]. Multiple lesions are frequently seen in TE patients, most commonly in the cerebral hemispheres and basal ganglia [41]. Tissue damage is not due to apoptosis since *T. gondii* actually induces an anti - apoptotic state in the infected cell [14].

Cytokines play a major role in the pathogenesis of *Toxoplasma gondii.* There is a strong experimental evidence that the manipulation of these cytokines can put forth a beneficial or damaging effect on the host and thus modulate the disease pathology. The importance of IFN-γ was clearly demonstrated

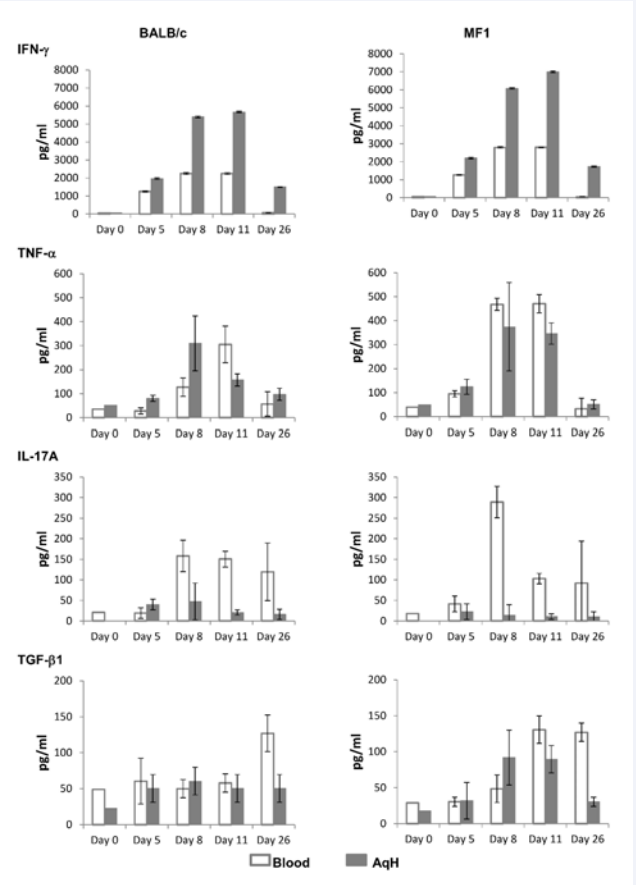

Figure 3 In vivo production of cytokines (IFN-γ, TNF-α, IL-17A, TGF-β 1) in serum and aqueous humour (AqH) following intravitreally injection of BALB/c and MF1 mice with 200 tachyzoites of type I RH Toxoplasma gondii strain. Serum and AqH were obtained at day 0, 5, 8, 11 and 26 post inoculation and cytokines levels were measured by colorimetric sandwich ELISA. The data is presented as pool of 10 infected BALB/c and MF1 mice. Values are the means of two independent experiments.

when the neutralization of IL-12 and of IFN-γ using anti-IFN-γ & anti-IL-12 MAb resulted in reactivation and loss of control on the parasite's multiplication leading to disease. Cytokine IL-27 was deemed as an endogenous suppresser on IL-17, the inflammatory cytokine that is capable of enhancing the inflammatory response in the brain. Although *Toxoplasma* is an intracellular pathogen thereby requiring a cell mediated immune response from the host, the cytokine IL-10 protects the infected mice from an exaggerated cellular immune response by inhibiting the production of pro - inflammatory cytokines: IL-12, IFN-γ, and TNF-β. Following Toxoplasma infection the host triggers a sequential balanced cytokine response to limit the infection and the disease pathology. However, cytokines can sometimes exert a negative effect on the host and augment the disease leading to severe irreversible tissue damage.

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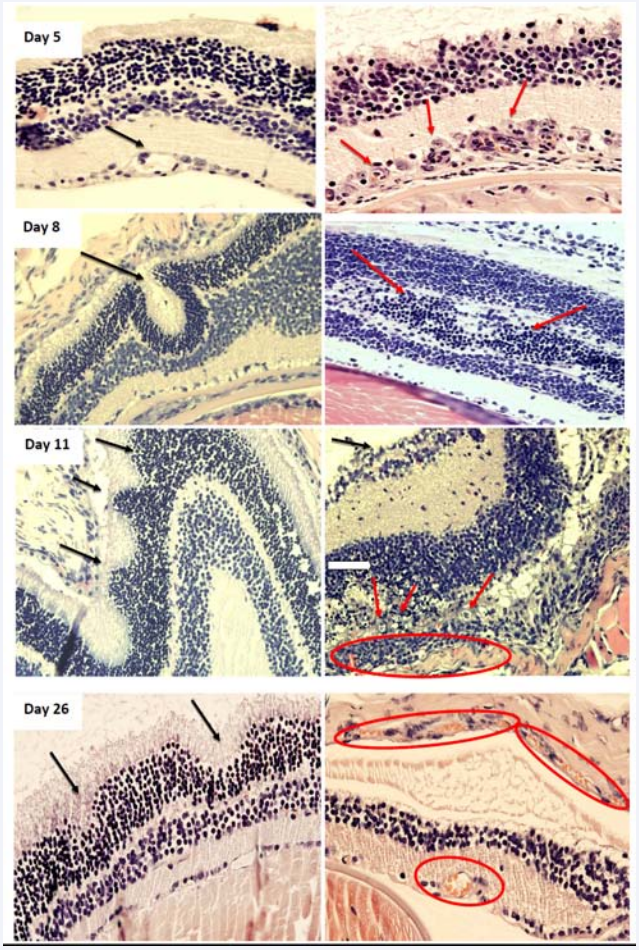

Figure 4 Light micrograph of eye sections, stained with hematoxylin and eosin, from BALB/c and MF1 mice following intravitreally injection with 200 tachyzoites of type I RH Toxoplasma gondii strain. A group of BALB/c (A) and MF1 (B) mice were sacrificed at the selected time points post - infection, eyes were enucleated, chemically fixed and processed as described in materials and methods. Figure panel A shows histopathology of retinal sections of BALB/c mice and panel B shows retinal sections of MF1 mice at a magnification of 40X and 60X.

Day 5 post-inoculation: (A) shows a dilated blood vessel with low infiltration of mononuclear cells (black arrow); (B) shows extensive clumping of ganglion cells with high infiltration of mononuclear cells (red arrows).

Day 8 post-inoculation: (A) a characteristic lacuna formation in the outer nuclear layer (black arrow); (B) shows the merging of the outer and inner nuclear layers and absence of the outer plexiform layer (red arrows).

Day 11 post-inoculation: (A) hump - like protrusions in the outer nuclear layer (black arrows) disrupting the rods and cones layer observed; (B) edema, alteration and thickening in the ganglion cell layer (black arrow, top left) deformation, merging of the outer and inner nuclear layers and absence of the outer plexiform layer (white arrow); extensive disruption of the rods and cones layer with presence of parasite tachyzoites (red arrows); alteration of the pigment epithelium layer and choroid with plenty of scattered red blood cells (encircled in red).

Day 26 post-inoculation: (A) small lacunae formed in the outer nuclear layer (black arrows) disturbing the rods and cones layer; (B) a dilated blood vessel in the ganglion cell layer (encircled in red, bottom) and extensive sledging of red blood cells within

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