The role of *Toxoplasma gondii* in Trigger an Autoimmune Disease

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Abstract: **Latent Toxoplasmosis is known as world- wide disease or infection caused by an intracellular mandatory protozoan: *Toxoplasma gondii* which is consider one of the important pathogen that can persist intracellularly lifelong in different tissues in the human body. An autoimmune disease is a condition arising from an abnormal immune response to a normal body part, the identification of etiological factors which include causation or/and originationof the induction of autoimmune disease has remained obscure despite a very extensive effort to analyze different factors that may be associated with autoimmune disease such as; the molecular structure of the target antigens and effector mechanisms. This review aimed to focus on the relationship between toxoplasmosis and autoimmune disease.**

***Keywords: Toxoplasma gondii*, Autoimmune Disease**

I. INTRODUCTION

Toxoplasma gondii is one of the important Eukaryotic zoonotic opportunistic pathogen with worldwide distribution. *Toxoplasma gondii* can infect chronically about One-third of the human populations in developed and developing countries. Toxoplasmosis is known tobe primarily transmitted via many pathways include; ingesting oocyst-contaminated food or water, utilizing raw or undercooked meat containing tissue cysts, vertical infection through the placenta from mother to fetus, different organ transplantation (liver, kidney) , and finally blood transfusion through infected donors during the active phase of the infection (1,2,3,4).

Many factors may play an important role in the increasing prevalence of toxoplasmosis in a community such as: geographical conditions or climate; high humidity was found to play an optimal condition for the sporulation and development of *T. gondii* oocysts, the second importantfactor depends on the habits of a community (food and health), finally the exposure to toxoplasmosis-associated risk factors by means having continues soil contact or having soil-related jobs (farmer) and eating raw vegetables or raw /undercooked meat at restaurants may increase the risk of acquiring the infection. (3,4,5).

Generally, when healthy individuals get infection with *T. gondii* are asymptomatic or induce only mild flu-like symptoms. On the other hand in immunocompromised patients *T. gondii* infections may lead to serious complications include toxoplasmic encephalitis which considers fatal disease and/or ocular toxoplasmosis which may result in the blindness of the patient if not treated in the proper way (6, 7).

In the United States, Autoimmune Disease (Ads) consider the third and the most common categorization of the disease after different cancer types and cardiovascular diseases which are a group of disorders of the heart and blood vessels, and about 14.7-23.5 million people affecting with this condition (5-8% of the population) (8,9). Moreover, the autoimmune disease may result from improper immune responses of the immune system to self-antigens. Still, the etiology of autoimmune diseases remains largely elusive but still, the most important factors or candidates include genetic abnormalities and infections (10). The frequency of autoimmune diseases has been increasing in developed countries over the last 20 years than in undeveloped ones (11).

Infections and autoimmunity

Many micro-organisms include viruses, bacteria and parasites are responsible for different infections and they know as important nature conditions or source for stimulating many of autoimmune diseases, moreover, the same disease can be developed by more than one pathogen or microorganism through the same pathological mechanisms such as molecular mimicry which means; the similarity between two or more microorganism, inflammation or irritation due to infection, antigen competition, super antigens which result in excessive activation of the immune response (8,9,10).

Moreover, there are many mechanisms have been developed by infectious microorganism and can cause different serious autoimmune diseases, these mechanisms are falling into two important sections: antigen-specific in which pathogen products or elements have a central role such in causing autoimmune disease such as; super antigens which are class of antigens that responsible for huge activation of the immune response or /and epitope (molecular) mimicry which is defined by the similarities between foreign and self -peptide and this similarity is enough to cause cross-reaction of autoreactive T or B cells by pathogen -derived peptides. The second section is antigen non-specific in which the microorganism provides the proper inflammatory setting for "bystander activation" which occur when CD8T, CD4T or B cells are activated in an antigen-independent manner. The most important mechanisms involved in autoimmune disorders are molecular mimicry and super antigens (10,11).

Toxoplasma gondiiinfection

The human can get the infection with toxoplasmosis by different methods or pathways such as eating raw or uncooked foods, drinking contaminated water with the parasite oocysts which is consider or contributed to their widespread dissemination (12). In 2012 Torgerson*et al*(13) supposed that foodborne toxoplasmosis was the second most common foodborne parasitic disease.

Despite toxoplasmosis can infect both healthy and immunocompromised humans and can infect about six billion people around the world it is still considered a neglected disease despite a high percentage of mortality and morbidity (14,15,16,17).

The most important point in the toxoplasma infection is that *Toxoplasmagondii* can interact with about 3000 genes or proteins in different host cells during the life cycle of the parasite in the host, and many of these genes represent an important *Toxoplasma gondii* host-pathogen interaction between them (12).

There are three important stages inthe life cycle of *T. gondii* which include: oocysts containing sporozoites, tachyzoites and bradyzoites (18). Moreover tachyzoites are known by their ability to infect almost all and only nucleated cells except red blood cells (RBC) not be infected. Moreover, the toxoplasmas are known by their ability to intracellular multiplication in different cells and avoid the phagolysosome, because these two important phenomena the parasite has the ability to lifelong existence in the host cells, so they will be a major reason for stimulation or activation of different autoimmune diseases (ADs)(8).Bradyzoites are known by their slowly and steadily division within cysts formed in the parasitophorous vacuole for the entire life of the host and this is possibly one of the important reasons to stimulate inflammatory response (8, 18,19). Subsequent oral infection, the parasite has the ability to crosses the intestinal epithelial barrier than will disseminate to the whole body host (20).

Accidently the cyst can be rupture in response to different external or internal stimulation, such as viral or bacterial infections. the bradyzoites will be convert to tachyzoites and this lead to infect or invade more new nucleated cells, while others are ingested by mononuclear cells (MNCs) which include different cells (T-cell, B-cells, NK cells) and induce an inflammatory response in the host (20).

The reactivation in low immunity patients who were formerly infected with *Toxoplasma gondii* led to low T-cell-mediated immune responses and this can make the reactivation of their past infection easier. The reactivation means the transformation of bradyzoites in the tissue cysts into rapidly proliferating tachyzoites; which may lead to severe complications and dissemination of the disease(20).

The latent toxoplasmosis was not considered important as acute and congenital toxoplasmosis, but many researchers found a relationship between many disorders in humans with latent toxoplasmosis which have been confirmed by case-control and cohort studies (20,21). So the positive serological result of those patients with latent toxoplasma with ordinary levels of IgG and low or undetectable concentrations of IgA and IgM anti-*Toxoplasma* antibodies, have been shown to reveal a higher likelihood or liability to suffer from different autoimmune diseases especially neuropsychiatric disorders (20,21).

The seroprevalence of IgG; ranged from 42% in Iran (22). In 2017 Amenah*et al*, was found that the rate of infection among students of science college was 27.6% (23). In Turky, Ertug*et al* found that among 423 pregnant women, 30.1% of them were infected with *Toxoplasma gondii*(24). On the other hand, in Western countries such as the United States, the prevalence of *Toxoplasma gondii*had declined from 14.9% in 1988–1994 survey to 9.1% in 2009–2010 survey (25). Also in France, the seroprevalence declined from 83% in 1965 to 37% in 2010 (25), this was attributed to the proper preventive measurement, high hygiene and cold climate (25).

The proposed mechanism behind the ability of toxoplasmosis to cause Autoimmune Disease

1-*Toxoplasma gondii*can cause infection and proliferation in humans byusing Heparan Sulfate (Hs) proteoglycans as receptors. Heparan Sulfate (Hs) proteoglycans have important role in the cells function such as cell cycle control; which include different cells phases, important cells function, division of many cells, transcription machinery which has important role in cell development and growth , chromatin construction alteration or modification, and transfer nutrient to the nucleus of the cell (26,27) .Moreover HS proteoglycans can be found in cell surface or within the extracellular matrix of the cells, as emulsifiable molecules in many human tissues and blood cells, finally can be found in the cell nucleus (8).

The HS receptors are composed of proteoglycans which are composed or built from glycosaminoglycan (GAG) chains and consider as important host cell receptors (28). The Tachyzoites active stage in parasite is composed of surface antigene 1 SAG1 and lectin which both can bind to HS proteoglycans (29,30). Bishop *et al* suggest that HS receptors help or facilitate parasite replication post-invasion (31). Moreover, Jacquet*et al* suggest that *T. gondii*can *expres*s an important surface antigen which is called SAG3 that can bind easily to HS receptor (29).

There are important roles for HS receptors in extensive infection or/and replication for *T. gondii*in different cell types in the human body. The HS receptors have important role in the replication of the Toxoplasma tachyzoites in the cytoplasm of different vertebrate cells. Moreover heparan sulfate can accelerate the replication of *T. gondii* in the parasitophorous vacuole. Importantly, much data showed that heparan sulfate does not act as a receptor on the cell surface but can also facilitate parasite replication (29,31). In addition to the previous component, the parasite composed of laminin which is implicated in important role in binding to the cell

surface, Furtado *et al* found that laminin which is found on the parasite surface can bind easily to laminin receptors on the many vertebrate cells and it is consistent with the ability of the parasite to enter or invade nearly all nucleated cells in human body (32). Moreover, the laminin in parasite surface can bind to host β1 integrins(32), Integrins are transmembrane glycoproteins that consist of an α and a β subunit and there function to act as the transmembrane bridge between the extracellular matrix which consist of (enzymes, glycoproteins, collagen) and the actin cytoskeleton which consists of actin and actin-binding protein and they responsible for the essential cellular process, so integrins can regulate the adhesive activity of different cells .when laminin in the parasite bind to the integrins this will facilitate attach and invade the tachyzoite in the cytoplasm of the host cells

Briefly, *T.gondii* can easily by different own structures infect almost all and only nucleated cells except RBC, and this can lead to intracellular division and life-long existence of the *Toxoplasma gondii* in the different host cells type. Moreover by using cellular heparan sulfate proteoglycans (HSPGs) and surface antigene type 1 (SAG1) as the parasite receptors which both of these structures can help the parasite to infect many cells type and proliferation in many cells in different tissues, this will help the parasite to control many cellular action or functions of human host cells from a diversity cell lineages and different tissues, all this may play an important role in the activation and development of several and many important autoimmune disease ADs.

2- The chronic infection with *T. gondii*may be highly related with many important molecules deficiencies in the cells such as iron, iodine and folic acid and this will accelerate development and/or progression many of autoimmune disease ADs

Toxoplasma gondii is known as autotrophs for many elements such as iron, cholesterol (33, 34), tryptophan (35), arginine (36), polyamines (37), purines (38), and other essential nutrients (39). The critical role that iron plays in many immune functions such as cell mediate immune response effector pathway and roles in cytokine and enzymatic activities make the deficiencies of the iron will be associated with mild immunosuppression and may inducing and/or progression of Ads. Moreover, Herqaux*et al* suggest that there is an interaction between the iron transporter which is called (natural resistance-associated macrophage protein 1(NRAMP1) and different autoimmune diseases, this protein(NRAMP1) was found to be implicated in resistance to intercellular infection and macrophage cells function in the human body, this protein has shown highly expressed in neuron cells of the human and microglial cells in the brain have an important role in control intracellular microbial replication by actively removing iron or other divalent cations from the phagosomal space (40). So when this important protein effect by different factors this will support the growth of the intracellular parasite.

In2003 Bowlus suggested that iron can catalyze the production of cryptic epitopes of several autoantigens; these cryptic epitopes are known as the source of autoimmunity, moreover, cryptic epitopes are part of proteins that are normally degraded during the antigen processing but may survive during this process as structure alteration of the proteins, and can cause potential role for iron in the accelerate and development of many important autoimmune diseases (41).

Chronic *Toxoplasma gondii* infection is highly associated with iron deficiency because this parasite needs additional requirement of iron for proliferation, this was support by Dimier& Bout they reported thatintracellular *T. gondii*replication relied on iron and this lead to inhibit the parasite replication by limiting the availability of intracellular iron to *Toxoplasma gondii* (42,43).

In summary, a combination of toxoplasma infection and iron deficiency is important in the development of different autoimmune diseases.

3- Exhaustion of the different immune system cells due to the chronic Toxoplasma infection

One of the important effects of T. *gondii*chronic infection is that the cytotoxic T lymphocyte will be exhausted and this will lead to losing their capacity to proliferate and lose the ability to intracellular killing, moreover the cytotoxic T cells lose the ability to produce cytokine and this will leads to development of different autoimmune disease

Many mechanisms have been developed by *T.gondii* to avoid or overcome the immunity against infection; Such as immune evasion which included: a) indirect mechanism by changing the regulation and excretion of many important immunomodulatory cytokines or by converting the ability of many immune cells to survive by interrogation with many different intracellular signaling pathways. In these different mechanisms, the parasite can overturn several important antimicrobial activity mechanisms of the host cells (44). In 2006 Christine*et al* suggest that toxoplasma has the ability to keep the balance between ordination and elimination of the host's immune response system to assure the survival of the host which is considered as a safe place for parasite development and growth (42). These mechanisms can help the parasite to persist lifelong in the human body. Moreover, in 2013 many researchers suggest that *T. gondii*has the ability to change the expression levels of important and viable host microRNAs in the host (12,45). This could lead to favour or prefer the growth of the parasite toxoplasma gondii and at the same time avoiding immune system, in order to survive and proliferate in the host lifelong. Moreover, the parasite can act in two directions which mean that the parasite can stimulate host immune responses and at the same time can effects various important host cell functions (8).

Plattner*et al*, also suggest that Toxoplasma profilin is necessary for host cell invasion and the profilin cab be

recognized by TLR11 in the host innate immune system. Moreover, profilin can plays an important role in parasite motility and acting as a microbial ligand so can be recognized by the host innate immune response. (46). In 2006 Bennouna*et al.,* showed that *Toxoplasma gondii* can inhibit Toll-like receptor 4 (TLR-4) linking in the host cells which has important role in recognition and elimination of the parasite and this lead to inhibit induced activation or movement of intracellular tumor necrosis factor-alpha (TNF-α) to the surface of peritoneal neutrophils in the host cells (47). In addition to all these mechanisms *Toxoplasma gondii* can change immune response towards TH2 lymphocytes which are known to have a significant role in humoral immunity reactions over TH1 which are known to have significant role in cell mediated immune responses in the host, toxoplasma can promote the excretion of anti-inflammatory cytokines, such as interleukin 10 (IL-10)and transforming growth factor alpha (TGF-β) so downregulation the development of the TH1 immune responses and render the macrophages ineffective in the human host system.

It is important to note that during acute infections with toxoplasma, T-cells play important role in the clearance of the parasite, but due to the different parasite mechanisms the T-cells will lose their ability to remove the parasite and become exhausted and at this point, the parasite enters the chronic phase.

During the chronic stage of infection which is known when the host is unable to fully clear toxoplasma and this may be due to dysfunction of the host immune system or/and because the ability of the parasites to escape from the immune system so this led to antigen-specific T cells become disfunction, exhausted and this lead to deleting these cells physically (48,49).

Exhaustion is definedby the constancy of antigen-specific- T cells in the host, which show impairment in their effector functions, deficient recall immune response to any infection and deficient in antigen-independent stability proliferation of the cells. All these mechanisms by toxoplasma led to exhausted cytotoxic lymphocyte and development of autoimmune disease the cytotoxic T cells will show decreased in their normal function, decrease in their ability to division, different cytokine production, finally loss their cytotoxic capability.

4- Cellular homeostasis can be maintained by two important processes; Autophagy and apoptosis which play an important role in physiopathology. The host immune system uses that two important mechanisms to remove or clear any intracellular microorganism and as a mechanism to observe and monitor pathogen invasion and any cellular alteration (50). Many autoimmune diseases are highly associated with dysfunction of autophagy such as rheumatoid arthritis diseases (51), neurodegenerative disorders such as multiple sclerosis and prion disease (52), inflammatory bowel disease such as ulcerative colitis (53), vascular disorders include (vein and arteries), and atherosclerosis heart disease (54). Moreover apoptosis has important role in inhibiting the division of invasive microorganisms so this will lead to protect uninfected cells and limiting damage to the host cell from pathogen

Many researchers have the spotlight on the relationship between the two important mechanisms; autophagic and apoptotic signaling pathways in different cells, which mean these two mechanisms act coordinately; autophagy acts as creator for apoptosis, and apoptotic signaling can cause activation of autophagy in the host cells (55,56,57,58).

Muniz-Feliciano *et al* found that *T. gondii*can resist and live by keeping away from lysosomal protease degradation in cells, it was reported that *T. gondii*may use different plans to keep away from autophagic targeting according to keep up non-fusogenic nature of the host vacuole (59). They reported that the parasite can activate epidermal growth factor receptor (EGFR) which prevent autophagy protein from killing the parasite (59)

In 2007 Carmen and Sinai suggested that theinteraction between *T. gondii*and multiple apoptotic regulatory pathways will lead tosuppressing the apoptotic response of host cell, so the host cell becomes resistant to apoptosis during an important stage of intracellular infection of the parasite which includes parasite spreading very fast, and parasite division in high number in the host cell, this will lead to the survival of the parasite in the host cell (60).

Thus, during the toxoplasma infection, both important processes pro- apoptotic and anti-apoptotic are dysfunctional, and this will lead to defect in the clearance process of the microorganism. In the same time the dispersed or removal of apoptotic leukocytes which infected by *Toxoplasma gondii* are not removed properly and this lead to the aggregate of these cells in different tissue in the host, this leads to progress inflammatory response and inflammation and this lead to activate different autoimmune disease (61,62). The aggregation of apoptotic dead cells lead to provoked different symptoms of inflammation and many autoimmune diseases (63).

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