Supervision of The Complement System by Toxoplasma During Neural Infections (A review)

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Abstract

Chronic infections with Toxoplasma gondii occur in the brain of mammalian hosts. The understanding of the relationship between Toxoplasma gondii, CNS, and the immune system assists in comprehending how Toxoplasma affects the complement system and how it exerts a defense mechanism against Toxoplasma. This review focuses on the supervision of the complement system by Toxoplasma gondii during neural infections. There are three possible mechanisms by which the protozoan can invade the brain. Tachyzoites in bloodstreams multiply, invade, and bind to endothelial cells before migrating into parenchymas via transcellular crossing mechanisms. Secondly, the immune cells become like the Trojan horse, which carries intracellular parasites across the blood–brain barrier (BBB). In the third mechanical process, the BBB can directly be crossed through the brain at the tight junction (TJ) by the tachyzoites. It is concluded that C3 manipulation of the integrity of the BBB can be used to increase T.gondii invasion into the CNS.

Keywords: Toxoplasma, Bradyzoite, Tachyzoite, Complement, Neural infections.

1. Introduction

The parasitic infections might be acquired from different environmental components such as soil, water sources, milk products or even from alimentary canals of some arthropods. Toxoplasma gondii is intestinal coccidian of felines; the definitive hosts and can infect a wide variety of intermediate hosts. In the warm-blooded animals and humans, infection is seen to be very common. It is found that one-third of humans are being exposed to the parasite. Al Se’adawy [1] found that 35% of aborted Iraqi pregnant women were due to toxoplasma infections. However, the infection rates by using ELISA were 35.4% using ELISA(IgG) and 6.25% using ELISA(IgM) [2]. It does not cause serious illness in other cases, but it can cause mental retardation and blindness in infected children and diseases in the immunocompromised individuals [3]. Humans can be considered as a carrier host for the whole life. A healthy immune system can help to prevent the parasite to cause illness. The complement system is the first line defense mechanism against the parasites [4]. This review aimed to explain the role of complement components during Toxoplasmosis.

2. Toxoplasma Gondii in Humans and Animals

Toxoplasma gondii; a zoonotic pathogen, is mainly responsible for causing infection in carnivore and omnivore animals including human [5]. This pathogen is mainly responsible for causing abortion in sheep. The infection could include other organs such as kidneys [6]. Toxoplasma gondii causes loss of vision and mental retardation in infected children [7]. There are three stages of its parasitic life which are oocysts, tachyzoites, and bradyzoites inside tissue cysts [8]. Domestic cats are the definitive hosts of Toxoplasma gondii. Cats excrete oocysts of Toxoplasma in their feces. Then, livestock and warm-blooded animals get infected by oocysts ingestion.

Ocular signs can be found in infected cats and dogs [9]. Infected sheep and goats during pregnancy may suffer from stillbirth, mummification, and abortion of the fetus [10]. Infected lambs are weak and unable to nurse [11]. Infection with Toxoplasma gondii can cause permanent changes in behavior of the host. Infection mostly occurs in stray animals and not in pet animals. No vaccine against this pathogen is available and the only possible way is to keep the pregnant animals away from the infected cats. In humans, infection can be reduced by consuming a well-cooked meat [11]. Infection in humans during the time of pregnancy is capable of causing congenital toxoplasmosis in infants and impairing the development of brain and retina. Neurological symptoms are the most common signs in Toxoplasmosis. In HIV/AIDS patients, the infection is...
reactivated and might cause coma and death [12]. Toxoplasmosis is not directly communicable to humans. The risk of infection can be reduced by good hygiene and proper food preparation [13]. In order to avoid infection, pregnant women should always wear gloves during gardening. Cats should be kept away from rodents and be fed on properly cooked food or commercial pet food.

Figure 1. Life cycle of Toxoplasma gondii. Adopted from (Centers for Disease Control and Prevention. (2018) Global Health, Division of Parasitic Diseases)

3. Transmission of Toxoplasma Gondii in Human and Animals

Toxoplasma gondii is a common worldwide parasite. Toxoplasmosis is transmitted through food, from animals to human, from mother to child and through organ transplantation (Figure 1). In infected pregnant women, Toxoplasma gondii passes on to the fetus through the placenta. The transmission of Toxoplasma gondii has three ways [14]. Firstly, through consuming oocysts in contaminated food and vegetable. Another way is by eating raw or not properly cooked meat or the transmission may occur through tissue transplant which contain the tissue cysts (bradyzoites) [15]. Earlier, the transmission was mostly caused by consuming raw or uncooked meat of pigs and sheep. However, due to farm management in recent years, the occurrence of the parasite in the animals producing meats has considerably decreased [16]. The last transmission route is through placenta to the fetus (figure 1).

Toxoplasma gondii is the main causative agent of zoonosis. Asexual stages of Toxoplasma parasites are found in the tissues of birds and animals. Toxoplasma gondii also reveals a coccidian-like life cycle. Toxoplasma has heteroxenous life cycle. The asexual development stage in various omnivorous or herbivorous intermediate hosts is followed by a sexual developmental stage in the intestine of the carnivorous definitive hosts, feline [17].

Several potential transmission routes had been evolved by the parasite. Toxoplasma gondii is capable to infect a broad range of host cells. The intermediate hosts are mainly warm-blooded animals while the definitive hosts are Felidae members [18]. Toxoplasmosis is transmitted by eating undercooked meat and shellfish, drinking unpasteurized goat's milk and eating food in the utensils that have been contaminated with raw food and shellfish [19]. Cats play a very important role in transmitting Toxoplasma gondii, cats get infected with the parasite by eating infected rodents and animals.

Cats spread the oocysts in the environment through feces. The accidental ingesting of the oocysts can cause parasitic infection. People can also get infected by drinking Toxoplasma contaminated water. The parasite can also be transmitted from a pregnant woman to her fetus through the placenta [20] which can cause abortion [1]. The signs of toxoplasmosis in unborn child can involve the nervous system and eyes. Toxoplasma can also be transmitted through infected blood transfusion or infected organ transplantation. In immunocompromised humans, an acquired Toxoplasma infection may cause reactivated toxoplasmosis ultimately leading to pulmonary disease. Toxoplasmosis is responsible for developing complications in transplantations of organ or bone marrow [22].
4. The Complement Role During Toxoplasmosis

4.1 The complement system

The complement system, a part of the immune system is activated by three pathways: classical, lectin and alternative. The classical pathway is started by antigen-antibody complexes with the help of antibody isotopes mainly IgG and IgM. The lectin pathway can be activated when certain structures such as carbohydrates bind to lectin molecules. The alternative pathway is spontaneously initiated. All the complement pathways converge with C3b convertase formation [23]. The C3 convertase split C3. The split C3 releases the C3b component which binds with the C3 convertase to generate the C5 convertase. The C5 convertase thus producing C5 [24]. The split products attract phagocytes to the place of infection and targets cells for the elimination by phagocytosis. The terminal pathway was initiated by the C5 convertase which in turn assembles the membrane attack complex (MAC). MAC then in turn creates a pore in the targeted cell membrane and subsequently causes cell lysis and death [24]. The activation of the complement systems is regulated by the complement control proteins such as factor H, properdin, complement factor H related proteins (CFHRs) and complement receptor protein (CR1) [23].

![The Complement System](image)

Figure 2. Complement Cascade. Figure supplied by Robert B. Sim, Oxford University (23).

4.2 The role of complement system during toxoplasmosis

Toxoplasma gondii can activate the complement through various mechanisms of host parasite relationships. The complement activation in most of in vitro experiments can destroy the protozoan. Presence of Toxoplasma antigens in blood circulation of adults can mediate complement activation. Toxoplasmosis has significant impact on the complement system, mediate the systemic inflammation with presence of antigen in the circulation. Toxoplasma gondii antigens in blood circulation of adults can mediate complement activation. Toxoplasmosis has significant impact on the complement system, mediate the systemic inflammation with presence of antigen in the circulation. Toxoplasma gondii antigens in blood circulation of adults can mediate complement activation. Toxoplasmosis has significant impact on the complement system, mediate the systemic inflammation with presence of antigen in the circulation. Toxoplasma gondii antigens in blood circulation of adults can mediate complement activation. Toxoplasmosis has significant impact on the complement system, mediate the systemic inflammation with presence of antigen in the circulation. Toxoplasma gondii antigens in blood circulation of adults can mediate complement activation.
being reported by some researchers that the complement activation protects the nerve cells in Status Epilepticus (SE) and epilepsy [34]. It is concluded that this mechanism used by T. gondii can protect the nervous cells.

The complement in conclusion is the two edged weapon that can be detrimental and beneficial for the host when the brain is being infected by T. gondii. The basal lamina, astrocytic end-feet, endothelial cells and pericytes comprised the blood–brain barrier (BBB) that are a selective barrier. In the BBB, the tight junctions (TJ) are adhesive structures which close the gap between the endothelial cells to prevent the entry of antigens and pathogenic microbes from blood into brain [35]. BBB should be crossed by pathogens for entering the Central Nervous System (CNS) which is a challenge [36]. It needs to be focused that how T. gondii crosses the TJ for entering into the brain. There are three mechanisms that have been proposed. Transcellular crossing mechanism shows that tachyzoites from blood streams can replicate, invade and adhere to the endothelial cells and breaks into parenchyma. The mechanisms were being discovered by using the multiphoton in transgenic reporter and in vivo imaging systems (Figure 3B) [37]. The CNS parasite infection precedes the infiltration of the immune cells [38]. It is being reported by some studies that the mouse brain is being infected more quickly by macrophages and dendritic cells infected previously with T. gondii tachyzoites [39]. The second mechanism is known as the Trojan horse like mechanism that involves infected immune cells become the carriers of intracellular parasites via BBB (Figure 3A) [39,40]. In the third mechanism, T. gondii tachyzoites can cross directly the BBB via the brain TJ (Figure 3C). It was being demonstrated that the T. gondii tachyzoites depicts “gliding motility” that can assist the parasites for going across the small intestine’s epithelium [41,42]. Tachyzoites under the shear force circumstances can follow the human vascular endothelium and increasing the invasive percentage [43]. The evidence line promotes to see if BBB was being crossed by T. gondii through the intracellular space. “Paracellular entry” was named by some scholars but no study has been published on the direct evidence for supporting it [44]. T. gondii was being hypothesized disrupts the BBB and it allows the T. gondii for passing by paracellular entry into brain in which C3 plays a significant role. It was being reported by previous studies reported that renal tubules barrier disrupted by C3 for developing proteinuria [45,46]. Blood-cerebrospinal fluid (CSF) barrier in brains is significant as BBB in which the choroid plexus epithelial (CPEpi) cells resents a significant component of the barrier. The CPEpi cell expresses importantly the C3a receptors (C3aR) of the C3 [47]. The myosin light-chain kinase (MLCK) is considered to be the main regulator of TJ permeability. MLck by adding C3 an increases transiently its phosphorylation [48]. Immunofluorescence was being proved by C3a for disorganizing the TJ of the mouse CPE. C3a effect was being found in the pulmonary and renal epithelium [45,49]. The effect represents online evidence for the hypothesis that TJ of BBB was being disrupted by C3a in the KM mouse brain during the infection. TJs are being consisted of transmembrane proteins includes intracellular protiens, claudins and occludins that maintains the integrity of BBB. The intracellular proteins include zonula occludens-2 (ZO-2), zonula occludens-3 (ZO3) and zonula occludens-1 (ZO-1) [50]. Protein kinase C (PKC) is necessary for the assembly of the TJs. The opening of the TJs was being affected by PKC and plays a significant role in increasing and decreasing the permeability of the TJ [51,52]. The phorbol 13-acetate 12-myristate as against of the PKC leads to TJs disintegration [53]. Constant PKa activation reduces the TJ proteins expression and increases the permeability of BBB that means that the functional barrier is missing [54]. HDEPS (Homogenous Differentially Expressed Proteins) in pathway of TJ were regulated down such as PKC. HDEP were being regulated and TJ protein ZO2 was seen to be one of them. The phenomenon can be compensatory impact of the TJ damage which was being caused by T. gondii infections that induces the down regulation of PKC for encouraging the secretion of TJ protein for restoring the TJ functionality. In C3, the pharmacologic interventions of the complement cascade have been discovered such the reactive airway disease [55] and autoimmune arthritis [56]. The findings have raised many questions. C3 manipulation of integrity of BBB can be employed for allowing the increase the invasion of T. gondii into CNS.

Figure 3. The routes of T. gondii’s brain infection.
The activation of the parasite through the placenta to the foetus within various host species. It can be vertically transmitted by tachyzoites which are being passed through the placenta to the foetus. As the classical complement initiates immune system, it can be applied to a number of pathogen related disorder. The complement may be triggered by different host parasite mechanisms offered by Toxoplasma gondii. The activation of the complement could kill the protozoan in most in vitro experiments. The classical pathway of complement can activate C1q during the chronic phase of Toxoplasma. C4 which is secreted and distributed in axons, synapse and dendrites by neurons is the significant feature of the complement cascade. Enhancement of C4b, C3 and C1q during Toxoplasmosis would induce nerve cell disruption such as synaptic loss, synapse and possible neurodegeneration.

**Conflict of interest**

I would like to declare that this review, titled (Supervision of the complement system by Toxoplasma during neural infections (a review)) is a personal non-profit work and there is no conflict of interest.

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