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Relationship between Toxoplasmosis and autoimmune disease

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Abstract

T. gondii is globally distributed with a high proportion of the world population estimated to be seropositive, and in the U.S. the parasite is responsible for approximately million infections each year. T. gondii tachyzoites infect almost all nucleated cells and their intracellular multiplication and lifelong persistence in the host cells play an important role in triggering and development of autoimmune diseases (ADs). Latent chronic T. gondii infection may be associated with iron, iodine, and folic acid deficiencies that facilitate development and/or progression of ADs. The oral route is the natural portal of entry for the parasite and gastrointestinal manifestations are frequently reported in patients with ADs. The parasite also triggers the secretion of antiinflammatory cytokines, such as IL-10, TGF-β, and generation of reactive nitrogen intermediates, thus suppressing the development of the TH1 immune responses and deactivating macrophages. Toxoplasma chronic infection-induced cytotoxic T lymphocyte exhaustion leads to development of ADs because of decreased polyfunctionality, cytotoxic capability, cytokine production, proliferative capacity, and metabolic deficiency. The process of CD4+ and CD8+ T-cell immune exhaustion inhibits the immune response, thus facilitating pathogen persistence. Systemic T. gondii infection triggers a rapid and persistent decrease in the size of naïve CD4+ T lymphocyte pool, and a long-term thymic atrophy and output due to destruction of the thymic epithelium. Chronic parasite infections characterized by lower pathogen burden usually restricted to tissues, suggest alternative driving forces in the induction of T cell exhaustion, such as parasite encystations. A significantly lower occurrence of antibodies to persistent viral infections reported in patients with some ADs compared with controls may be due to suppressed (exhausted) function of host B cells. Both T. gondii- and viral-associated inflammatory processes may be mutually overlapping which lead to worsening or improving clinical course of ADs depending on final temporary or stable proinflammatory/ antiinflammatory cytokine constellations. Dual-affinity T cell receptors may partly be responsible for frequently observed coinfections of T.gondii with some viruses and bacteria. Commonly reported comorbidities in ADs may at least in part be explained by liver damage caused by the pathogen.

Introduction

Toxoplasmosis is a neglected, opportunistic disease and the intracellular parasite is highly pathogenic especially for immunocompromised subjects[1-2]. At present, in immunocompetent persons T. gondii infection is believed to be asymptomatic[2,3], but a steadily increasing body of literature data strongly suggests that the pathogen is emerging as a neglected global health threat[1,3], also in immunocompetent individuals.

Worldwide, over six billion people have been infected with T. gondi and IgG seroprevalence against the parasite varied from 6.7% in Korea[4], 47% in France, to 98% in some regions. In the United States, T. gondii is responsible for approximately million infections each year, and the overall antibody seroprevalence among individuals ≥ 6 yrs of age in 2011-2014 was 11.14% (95% CI 9.88% - 12.51%). The frequency of infection increased significantly with age in persons aged 66-75 years. The parasite is omnipresent, and exposure to kittens and raw or uncooked foods were the main risk factors for T. gondii infection in the United States. Contamination of drinking water with the parasite oocysts also contributed to their widespread dissemination.

Discussion:

1-VASCULAR ENDOTHELIAL CELLS ARE SUS- CEPTIBE TO PERSISTENT INFECTION WITH T. GONDII TACHYZOITES AND THEREFORE MAY PARTICULARLY FAVOR DEVELOPMENT OF ADs

The endothelial cells are critically important for the delivery of nutrients and oxygen throughout the body, but they also contribute to pathology including the triggering and persistence of inflammation[5]. T. gondii is disseminating in the body in a Trojan horse-manner in various eukaryotic cells, including endothelial cells and macrophages, and division rate of intracellular unprimed T. gondii tachyzoites in endothelial cells, monocyte-derived macrophages, peritoneal, or alveolar cells is rapid [7].

Canedo-Soares et al[8] analyzed invasion kinetics of two T. gondii strains, RH (virulent) and ME49 (nonvirulent) in two human vascular endothelial cell types, HMEC-1 (skin microvasculature) and HUVEC (umbilical cord vein vasculature) and established that surprisingly the less virulent strain invaded a greater proportion of cells than the more aggressive RH strain. Similar results were obtained by Lachenmaier et al who showed in vitro that RH tachyzoites invaded lower proportion of rat brain microvascular endothelial cells than those of ME49 strain. Thus, it appeared that T. gondii virulence relied more on its replication speed than on its invasion efficiency[8].

Smith et al[6] found that retinal vascular endothelium cells have enhanced susceptibility to infection with T. gondii tachyzoites in comparison with aorta (55% more), umbilical vein (33%), and dermal endothelial cells (34%). Free tachyzoites had the ability to transmigrate a stimulated human retinal endothelium monolayer[9]. Tachyzoites crossed in vitro retinal endothelium assisted by intercellular adhesion molecule-1 (ICAM-1) (the cell surface IgG immunoglobin superfamily member), and ICAM-1 blockade significantly inhibited the parasite migration across stimulated human retinal, but not choroidal vascular endothelium[9]. There has been interest in the heterogeneity of vascular endothelium, not only between arteries and venous types[10], but also between same type vessels located within different organs or within different tissues in the same organ.

2-AUTOIMMUNITY AND GASTROINTESTINAL TRACT DISORDERS

Underestimated role of oral T. gondii infection in development of gastrointestinal manifestations frequently reported in ADs Gastrointestinal manifestations are often documented in many systemic ADs including SLE, RA, Sjögren's syndrome, Behçet disease, progressive systemic sclerosis, polyarteritis nodosa, inflammatory muscle disorders, antiphospholipid antibody syndrome, thyroid diseases, primary biliary cirrhosis, and ASD[11].T. gondii exposure is the well-documented risk factor for schizophrenia[12,13], inflammatory bowel disease, ulcerative colitis, celiac disease, autism, and Leśniowski-Crohn's disease[14]. Interestingly, in a large sample of 23 471 primary care patients (mean age 51.4 yrs, 66.1% female) studied recently it was found a significantly increased prevalence of ADs in functional gastrointestinal tract disorders not explained by differences in age and gender[15]. This may support a notion that T. gondii infection play a much more important, but so far neglected, role in the pathogenesis of ADs[14]. The oral route is the natural portal of entry for T. gondii. Enterocytes are the first cells to be invaded by the parasite when ingested pathogens are released from cysts or oocysts within the gastrointestinal tract[16,17,18].The intestinal epithelium and the underlying mucosal tissues, as well as local lymph nodes with lymphatic endothelial cells (LECs) are heavily populated with immune system that can make rapid contact with the parasite following intestinal penetration, and there was a protective mucosal TH2 immune response against T. gondii [19]. Lymphatic vessels are key routes for the recirculation of fluid and cells that enter tissues from blood vessels[20]. LECs line the afferent and efferent lymphatic vessels, the medullary sinuses, and both the ceiling and floor of the lymph nodes[21]. The gaps between LECs are so large that bacteria and other cells can enter along with the fluid. DCs, macrophages, and lymphocytes enter lymphatics, but neutrophils and erythrocytes generally do not[20]. Recently, it was demonstrated that LECs have antigen presenting cell properties because they express MHC I and MHC II molecules on the cell surface, and frequently they are presumed to be the first that encounter peripheral antigens, cytokines and immune cells[21,22]. LECs probably are able to directly present antigens to CD8+ T cells

during the early phases of inflammation and indirectly by DCs through archiving of antigens[23,24]. Enlarged mesenteric lymph nodes frequently seen at imaging in patients with inflammatory bowel disease, children with abdominal pain, and in asymptomatic children may be due to T. gondii infection[14]. This suggestion is supported by the finding that DCs can move to Peyer's patches and mesenteric lymph nodes where they interact with naïve lymphocytes and initiate adaptive immune response that result in activation of T and B memory cells, and proliferative response and cytokine release, finally leading to gastrointestinal tract inflammation[14,25].

3-POSSIBLE LINK BETWEEN THE INCREASED SERUM AUTOANTIBODIES AGAINST LAM- ININ IN PATIENTS WITH SEVERAL ADs AND CHRONIC T. GONDII INFECTION

Autoimmunity against laminins has been described in several ADs including vasculitis, connective tissue diseases, mucous membrane pemphigoid, and antilaminin g1 pemphigoid, cutaneous lupus erythematosus, scleroderma, and psoriasis, and all these diseases were found to be associated with pathogenic role of antilaminin g1 autoantibodies[26].Laminins are a family of glycoproteins present in the extracellular matrix and the major constituents of basement membranes, and integrins (aβ transmembrane receptors) act as receptor for laminins. The a6β1 integrin is the major leukocyte laminin receptor on macrophages, neutrophils, endothelial cells of large blood vessels, and T cells[27]. Cell adhesion molecules, integrin a6β1 and intercellular adhesion molecule (ICAM)-1 were implicated in tachyzoite binding to host cells. Soluble host laminin can associate with the surface of extracellular parasites. This adherent laminin is then available to interact with integrin a6β1, creating a molecular bridge between parasite and host cell. Human ICAM-1 recognizes the parasite adhesive microneme protein MIC2 that is liberated onto the surface of the parasite prior to host cell invasion. Furtado et al found that laminin, an extracellular matrix protein, increased T. gondii attachment to the murine macrophage cell line J774 in a dose-dependent fashion. It was also demonstrated that tachyzoites bearing surface laminin bind to multiple laminin receptors in attaching to different target cells. These suggestions may be supported by the report that among 413 patients with inner ear disorders of unknown etiology, serum antilaminin antibodies were found in 68% of individuals with sensorineural hearing loss. Other authors also documented that toxoplasmosis was associated with sensorineural hearing loss in children. Similar associations were found

between the increased titers of serum autoantibodies against laminin in patients with systemic sclerosis, and in individuals with SLE, and the elevated serum IgG against T. gondii in these two clinical entities. It must be noted that serum anti-toxoplasma antibodies were markedly increased also in patients with antiphospholipid syndrome, and endothelial cells appeared to be the target for antiphospholipid antibodies, likely leading to a procoagulant state[28]. Nb. human endothelial cells are known to be activated by IFN-γ to inhibit T. gondii replication. In addition, an association of IgG antilaminin-1 autoantibodies with endometriosis in infertile patients, and with women having recurrent miscarriages, have been reported, and T. gondii infection is known to impair reproductive function in animals. The above-presented arguments are very important and may be supported by the significantly increased levels of antilaminin autoantibodies in nonautoimmune individuals with acute parasitic infections ,frequently reported problems with infertility in persons suffering from various ADs, pregnancy loss and endometriosis and T. gondii worldwide dissemination in animal and human populations.

4-DOWN-REGULATION OF B AND NK CELLS, NEUTROPHILS AND MACROPHAGES DEFENSE RESPONSES DURING T. GONDII IN- FICTION

A significantly lower occurrence of antibodies to persistent viral as well as T. gondii infections reported in patients with some ADs compared with controls may be due to suppressed (exhausted) function of host B cells. These cells contribute to disease pathogenesis in autoimmunity and also play an immunomodulatory role in regulating the immune response by secreting cytokines that inhibit disease onset and/or progression. It was found that pathogenicity of T. gondii increases through B2 cell-mediated downregulation of host defense responses[29], and Flegr & Striz demonstrated that lymphocyte B-cell counts were significantly reduced in both males and females with toxoplasmosis as compared with controls.B cells (also known as B2 cells) play a significant role in development of several ADs, including RA, SLE, vasculitis, myositis, MS, Sjögren syndrome, blistering skin disease, and chronic lymphocytic leukemia. These cells positively regulate immune responses through antibody production and CD4+ T cell activation[30].B cells can function as antibody-producing cells and they can also modulate immune responses through critical secretion of cytokines and chemokines, as well as antigen presentation[31]. B cells (innate-like B cells) are activated during T. gondii infection because they generated short-lived plasma cells providing a prompt antibody source, and also

induce massive B cell response that leads to hypergammaglobulinemia with production of serum specific for the parasite and self and/or not related antigens[31].B cell exert suppressive functions in infectious diseases because neutralizing antibody production by B cells and cytotoxic activity of CD8+ T cells are well accepted components of the adaptive immune response of the host to viral infection. Chen et al demonstrated that B1 cells play an important role in host protection against T. gondii infection since high expression of both TH1- and TH2-type cytokines and a high level of NO production in T. gondii-infected B cell-deficient mice transferred with primed B1 cells. However, B cell-deficient mice have a decreased resistance to infection with the parasite despite unimpaired expression of IFN-γ, TNF-α, and iNOS. . Because B cells can directly modulate also DC and T-cell subsets that affect adaptive immunity and the progression of infection, they may play both a protective and a pathological role in the host.The parasites have evolved unique ways to evade B cell immune responses inducing apoptosis of conventional mature B cells and MZ B cells[31]. Moreover, it was suggested that during many chronic infectious diseases, such as for instance HIV-AIDS, tuberculosis and malaria, immune activation and inflammation drive a large expansion of exhausted B cells (atypical memory B cells or tissue-like memory B cells) that contribute to deficiencies in the acquisition of humoral immunity. Strickland & Sayles found that T. gondii infected mice immunized with sheep red blood cells had a depression not only in the primary, but also in the secondary humoral immune response, since they showed less IgM and IgG splenic antibody-secreting cells than non-infected control animals. This indicate that the parasite not only affected development of the cells involved in antibody production but also disturbed an already established humoral response against other pathogens through memory B cells. This reasoning may be supported by the significantly lower occurrence of antibodies against T. gondii and some other pathogens in the sera of diabetic patients compared with their family members or healthy controls, probably due to their impaired innate immune B cell aInhibitory receptor profile of T cells in the parasite and two different models of exhaustion. capacity associated with persistent infections with these microbes . These findings are also in line with the markedly lower levels of immunoglobulins IgG1, IgG2a, IgG2b, IgG3, IgA, and IgM secreted by murine splenic lymphocytes infected in vitro with T. gondii tachyzoites. Moreover, low maternal anti-Toxoplasma IgG antibody was associated with increased offspring odds of autism[660], and several parental ADs were correlated with ASD in offspring[33].

Conclusion

All presented literature data may suggest that T. gondii is the chief of the criminal gang responsible for triggering, development and clinical course of several ADs. This recommendation is supported by the following facts: a) approximately 30-50% of the world population is infected with the parasite, b) the pathogen was detected in patients with various ADs, c) T. gondii have a plethora of antigens at its disposal that can attack host protein and carbohydrate substances resulting in development of antibodies and autoantibodies to self antigens and enhancing immune responses to nonself antigens, d) specific molecules of the microbe manipulate multiple strategies to downregulate innate and acquired defense immune responses of the host, e) T. gondii in the host may act in the form of tachyzoites and/ or bradyzoites, being present intracellularly and/or circulating in the blood, and attacking all nucleated cells, particularly endothelial cells, as well as affecting bystander cells, thus leading to development of various organ-specific and organ-nonspecific clinical entities. Dual activity of the parasite to both promote and inhibit cell apoptosis and impaired clearance of autophagy proteins that serve as a persistent source of foreign antigens favor development of autoimmunity.

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