GV-SOLAS
Gesellschaft für Versuchstierkunde
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Expert Information

from the Working Group on Hygiene

Implication of infectious agents on results of animal experiments

Toxoplasma gondii

(description for intermediate hosts)

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Contents

Toxoplasma gondii

Background

- Toxoplasma (T.) gondii was initially described more than 100 years ago in Tunis in the tissues of the gundi (Ctenodoactylus gundi), a North African rodent, and in Brazil in the tissues of a rabbit. T. gondii is a ubiquitous, Apicomplexan parasite of warm-blooded animals that can cause several clinical symptomes including encephalitis, chorioretinitis, congenital infection and neonatal mortality. Fifteen years after the description of T. gondii a fatal case of toxoplasmosis in a child was reported. In 1939 T. gondii was for the first time conclusively described as a cause of human disease. It was not until the 1960s and 1970s that the parasite was identified as a coccidian. Cats were identified as the definitive host by several groups working independently.[1]

Prevalence

- The prevalence of natural infection in laboratory mouse facilities is negligible, because laboratory mice no longer have access to sporulated cysts shed by infected cats, which were historically the major source for cross-infection.[2]
- In Uganda, Africa 47% of 85 tested free-range chicken were *Toxoplasma* antibody positive.[3]
- In Vietnam, *Toxoplasma* antibodies were found in pigs in 75 of 325 (23%) finishers, 63 of 207 (32.3%) sows, and 22 of 55 (40%) boars.[4]
- 46% of 84 free-range chicken in a study conducted in Brazil were *Toxoplasma* antibody positive.[5]
- Antibodies to *T. gondii* were found in 52 of 101 (51.5%) dogs tested in Durango City, Mexico.[6]
- *Toxoplasma* was also found in wildlife animals like the Hawaiian monk seal[7] or the artic fox (*Vulpes lagopus*).[8]

Host species

- Members of the cat family (*Felidae*; definitive host).[9]
- All laboratory and domestic animals, birds and humans are intermediate hosts.[10]
- Different host species susceptibility.[11,12]

Properties

- *T. gondii* is an obligate intracellular parasite capable of infecting almost all warm-blooded animals and humans.[9] The three infectious forms of the parasite are: (1) the rapidly dividing tachyzoite, responsible for systemic invasion during primary infection, (2) the slowly growing bradyzoite associated with chronic infection, and (3) the sporozoite, sexually produced in oocysts.[11]
- Despite having a broad host range, *Felidae* (mainly house cats) are the only hosts in which sexual development is known to take place. Development of gametocytes within intestinal epithelial cells culminates in fertilization and shedding of infectious oocysts with faeces. These spore-like particles can contaminate water and food and lead to infections of a wide range of animal species. In the intermediate host, the

ability to undergo asexual replication, in the form of fast-growing tachyzoites that replicate within nucleated host cells, allows the parasite to rapidly increase in number and disseminate throughout the body. Following a vigorous immune response, the parasite differentiates into semi-dormant tissue cysts that harbour slow growing bradyzoites. Predation and ingestion of tissue cysts by cats completes the cycle.[10]

- Persistence of *T. gondii* may lead to physiological and behavioural consequences in infected rodents, resulting in reduced fear of Felidae, their natural predators[9,13-18], as well as decreased[19] or higher activity level.[20]
- After host cell invasion, parasites replicate quickly (known as tachyzoites) by endogeny that leads subsequently to the lysis of the infected cell and spread to neighbouring cells. The parasite is able to cross the intestinal epithelial barrier, disseminate throughout the body, and localize in the muscle, placenta, brain, or eye. Transmigration across polarized epithelial cells is highly associated with the parasite genotype and virulence. Toxoplasma is also able to cross the blood-brain barrier. Ultimately, immune pressure on the protozoan results in the formation of cysts, containing the slow replicating form (bradyzoite) in neuronal tissues and skeletal muscles to establish latent infection.[21-23]

Susceptibility

- Although wild rodents, including house mice, are relatively resistant, laboratory mice are highly susceptible to infection.[24]
- Differences in genes within the H-2 and H-13 region correlate with resistance or susceptibility to development of *Toxoplasma* encephalitis in mice.[25-28]
- Age, gender, and pregnancy influence susceptibility to *T. gondii* infection in mice. 2-3 months old hybrid mice are more resistant than 22-24 months old hybrid mice, non-pregnant BALB/c females are more resistant than pregnant BALB/c females, male SCID mice are more resistant than female SCID mice.[29-31]

Organotropism

- In definite hosts (*Felidae*) shizogonic and gametogonic stages develop usually in the ileum, although the entire length of the small intestine can be affected.[32]
- In intermediate hosts, tissue cysts are predominantly located in the brain and other neural tissues, but they also regularly occur in skeletal muscles, heart, tongue and, at least in some host species, in visceral organs such as lung, liver or kidney.[33]

Clinical disease

- Usually inapparent (e.g. in rats, cattle, horses, pigs, goats or sheep).[12]
- Severe symptoms and/or febrile disease occur in some species (e.g. marsupials, monkeys, mice).[12]
- Toxoplasmosis can cause necrosis and granulomatous inflammation in the intestine, mesenteric lymph nodes, eyes, heart, adrenals, spleen, brain, lung, liver, placenta, and muscles.[2]

Pathology

- Central nervous system: parasite tissue cysts are found in all brain areas of mice, prior studies reporting high numbers located in the amygdala and frontal cortex.[34-37]

- Lesions in immunocompromised mice may lack inflammatory infiltrates and solely consist of small necrotic foci and scattered cysts.[38,39]
- Human cells are destroyed by active multiplication of *T. gondii*. Infection may result in necrotic foci. Congenital infection often involves retina and brain; focal chorioretinitis may result in impaired vision. Brain involvement in immunosuppressed human patients may lead to large necrotic abscesses.[40]

Morbidity and mortality

- Largely depending on the route of infection, parasite strain and dose, and the immunologic state of the host. Mortality in BALB/c and DBA/2 strains was 100% on day 12 and 13 of infection. A hundred percent of mice of the B1O.D2 strain died by day 19. Mortality in C57B1/6J and C3H/Bi mice was intermediate, 87 and 80%, respectively. Mice of the DBA/1 and white SW/SIM strains were most resistant, with a mortality of 67% at day 30 after infection.41
- One to 10 oocysts of the M-7741 and the Aldrin Toxoplasma strains killed orally inoculated mice, whereas up to 1,000 oocysts of the BWM and the S-1 strains caused inapparent infections.42,43
- Thirty weeks after infection, 64% of CBA/Ca mice infected with the ME49 Toxoplasma strain had died. In contrast, none of the mice infected with the DAG strain had died.[44]

Zoonotic potential

- *T. gondii* is found in humans worldwide, under a variety of climates and socio-economic circumstances. It is estimated that one third of the world's human population is chronically infected with this parasite. T. gondii infections cause significant morbidity and mortality worldwide with a wide spectrum of clinical manifestations both in immunocompromised and immunocompetent hosts. Transmission to humans occurs by ingestion of oocyst-contaminated soil and water, from tissue cysts in undercooked meat, by transplantation, blood transfusion, laboratory accidents, or congenitally.[11,44,46]
- Acute primary infections in pregnant women can have devastating sequelae and can lead to congenital toxoplasmosis with severe neurologic or ocular manifestations and even death.[46]
- Undercooked meat, especially pork, lamb, and wild game meat, are sources of foodborne transmission for humans. The new trend in the production of free-range organically raised meat could increase the risk of *Toxoplasma gondii* contamination of meat.[47]

Interference with research

Oncology

- The interplay between *T. gondii* infection and tumor development is intriguing and not yet fully understood. Some studies showed that *T. gondii* reversed tumor immune suppression, while some reported the opposite, stating that *T. gondii* infection promoted tumor growth.[48-50]

Teratology

- No data

Infectiology / Interactions with other infectious agents

- Macrophage clearance and killing of *Listeria monocytogenes* and *Salmonella typhimurium* are decreased in mice infected with *T. gondii*.[51]
- Infection with murine leukemia virus may lead to reactivation of chronic *T. gondii* infection.[52,53]
- Mice infected with *T. gondii* are resistant to proliferation of *Cryptococcus neoformans* cells in the brain.[54]

Immunology

- Acute and chronic *T. gondii* infections modulate the immune responses in mice.[39]
- *T. gondii* is able to induce transient immune downregulation.[55-58]
- *T. gondii*-infected cells are resistant to multiple inducers of apoptosis.[59]
- Gamma delta T-cells induce expression of heat shock protein 65 in macrophages of mice infected with *T. gondii*, thereby preventing the apoptosis of infected macrophages.[60]
- Intracellular *T.* gondii interferes with the MHC class I and class II antigen presentation pathway of murine macrophages.[61]
- CD4+ and CD8+ T-lymphocytes appear to act in concert to prevent reactivation of chronic *T. gondii* infection.[62-64]
- NK cell activity and production of IFN gamma are increased during the course of *T. gondii* infection in mice; IFN gamma plays a critical role in preventing cyst rupture and toxoplasmic encephalitis.[65-68]
- Cytokine levels are elevated in infected humans and in murine models of toxoplasmosis. Several publications describe the immunopathology of *T. gondii* infection in humans.[69-73]
- IL-12 is crucial for the generation of both innate resistance mechanisms during the acute phase of infection and T-cell-dependent acquired immunity during the chronic phase.[74]
- Various other cytokines, such as IFN-β, IL-1, IL-4, IL-6, IL-10, TGF-β and TNF-α, are implicated in the pathogenesis of *T. gondii* infection.[69,75-84]
- Inducible nitric oxide is essential for host control of chronic *T. gondii* infection.[85]
- Innate resistance mechanisms during *T. gondii* infection are reviewed by Alexander et al.[86]; T cell-mediated immunity during *T. gondii* infection is reviewed by Denkers and Gazzinelli.[87]

Toxicology

- *T. gondii* infection increases toxicity of some drugs in mice (e.g. neostigmine).[88]

Physiology

- Mice infected with *T. gondii* exhibit ovarian dysfunction with uterine atrophy and thyroidal dysfunction (decline in serum thyroxine levels), probably due to impaired release of hypothalamic releasing.[35,89,90]

Cell biology

- Cell invasion by *T. gondii* into murine cells involves the concerted action of protein secretion along with actin-based motility.[10]

Assisted reproductive technology

- No data

Special considerations

- Quarantine and testing of all incoming animals from non-commercial sources is recommended

Updated by Thomas Kolbe, Vienna, November 2024

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