

Immune Response to Toxoplasmosis and Evasion

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Toxoplasma gondii(con)

- The name *Toxoplasma* is derived from the Greek word 'Toxon' meaning **arc** or **brow** referring to the *curved* shape of the trophozoite. *Toxoplasma* is now recognized as the **most common protozoan parasite globally**, with the widest range of hosts spread over **200 species** of birds, reptiles, and mammals, including humans.

Toxoplasma gondii

Host

Mainly domestic and wild cats.



Intermediate host

- Human, birds, pigs, rodents, and sheep.



Morphology

- *T. gondii* occurs in 3 forms
- Trophozoite.
- Tissue cyst
- Oocyst.
- The trophozoite and tissue cyst represent stages in asexual multiplication (**schizogony**), while the oocyst is formed by sexual reproduction (**gametogony or sporogony**). All 3 forms occur in domestic cats and other felines, which are the **definitive hosts** and support both schizogony and gametogony.

Toxoplasma gondii exists in three forms

All parasite stages are infectious.

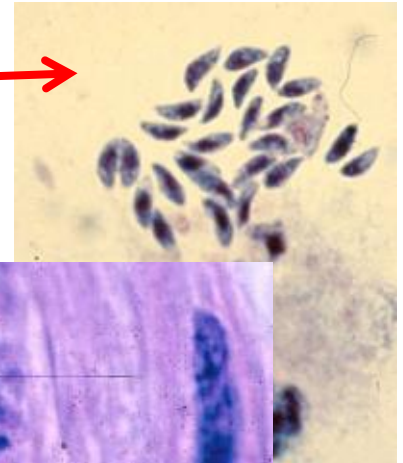
1. TACHYZOITES

2. TISSUE CYSTS

3. BRADYZOITE

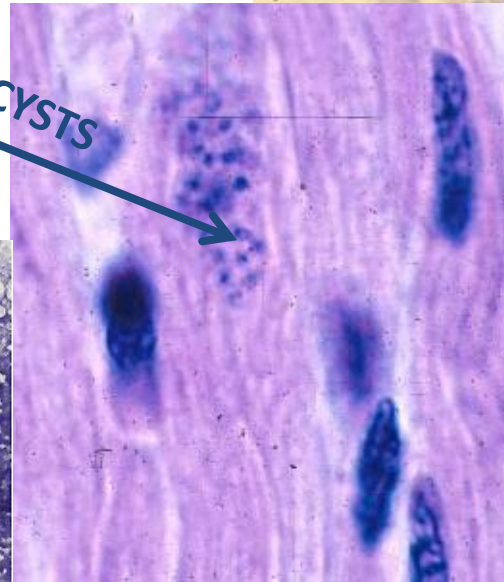
4. OOCYSTS

Tachyzoites



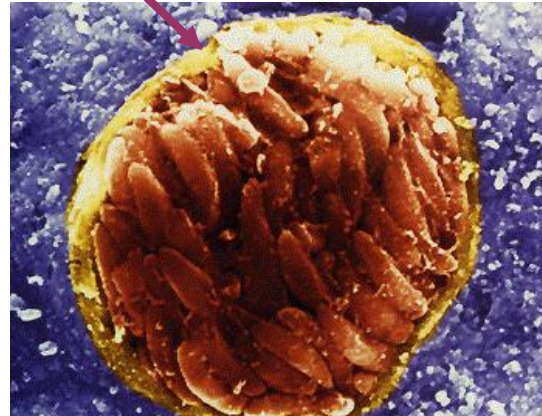
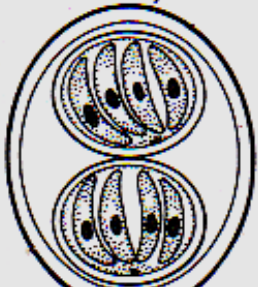
Bradyzoites

TISSUE CYSTS



Oocysts

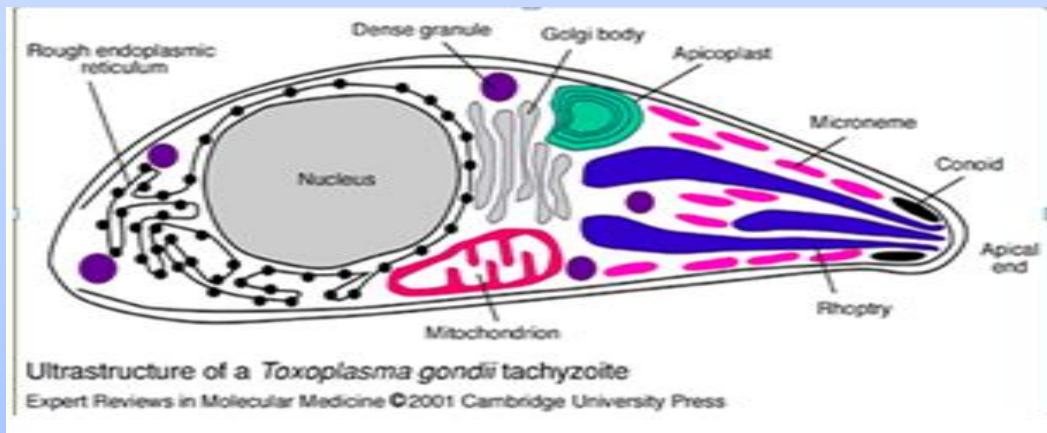
Sporulated oocyst



- Only the asexual forms, trophozoites and tissue cysts are present in other animals, including humans and birds, which are the intermediate hosts.
- All the 3 forms are infectious to man.

Trophozoites (Tachyzoites)

- *Trophozoites (Tachyzoites)*
- The trophozoite is **crescent** shaped , with one end pointed and the other end rounded .It measures **3–7 μm** in length. The nucleus is ovoid and is situated at the **blunt end** of the parasite .Electron microscopy reveals an **apical complex** at the pointed end



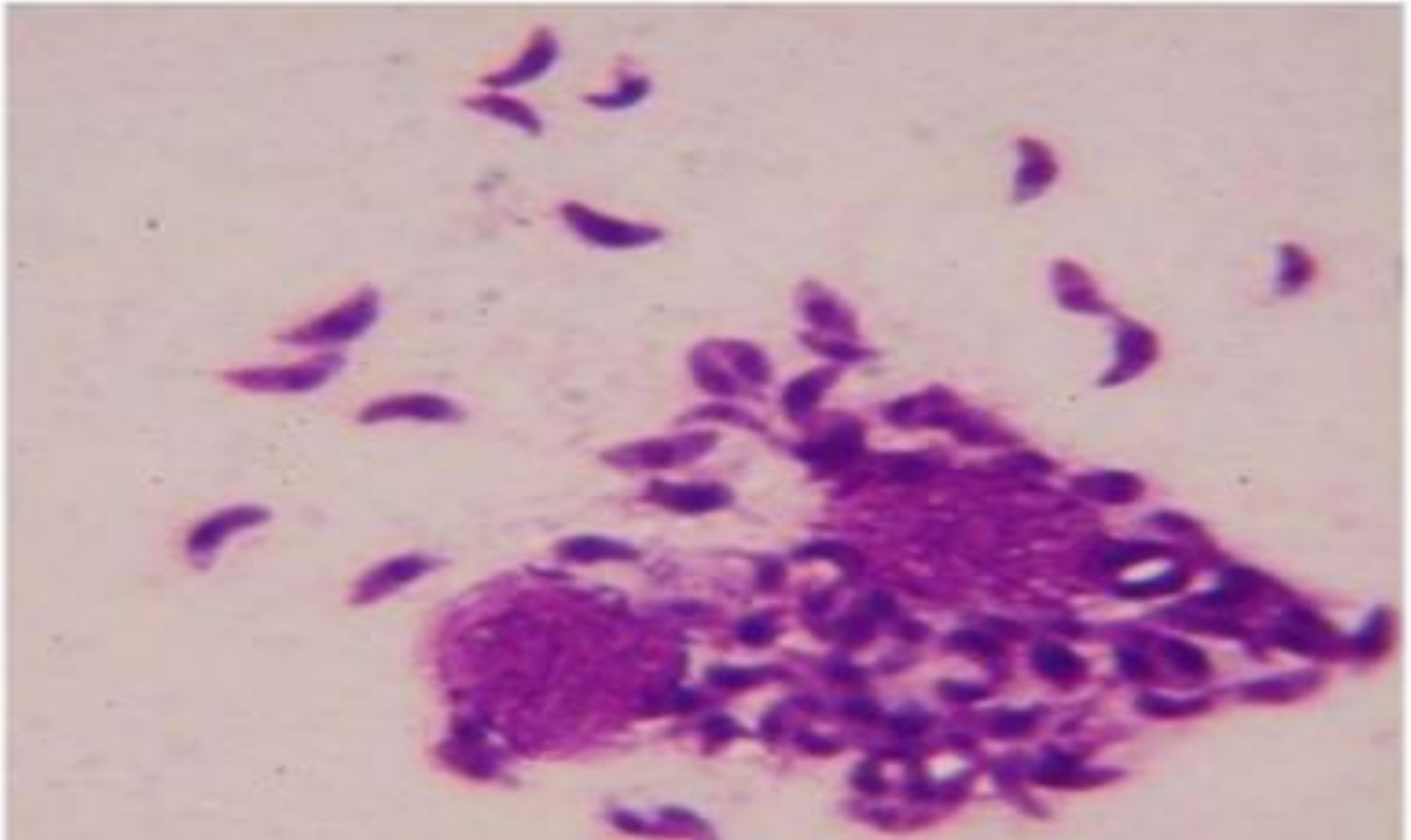
Tachyzoites(con)

It can invade any **nucleated cell** and replicate within cytoplasmic vacuoles by a process called **endogony (internal budding)**, where in **2 daughter trophozoites** are formed, each surrounded by a membrane, while still within the parent cell. When the host cell becomes **distended** with the parasite, it **disintegrates**, releasing the trophozoites that infect other cells.



Tachyzoites

Image of a tachyzoite



Tissue cyst

- Tissue cysts are the **resting** form of the parasite .They are found during **chronic stage** of the infection and can be found in the **brain** (most common site),skeletal muscles, and various other organs .The cyst wall is **eosionophilic** and stains with **silver**, in contrast to the pseudocyst.

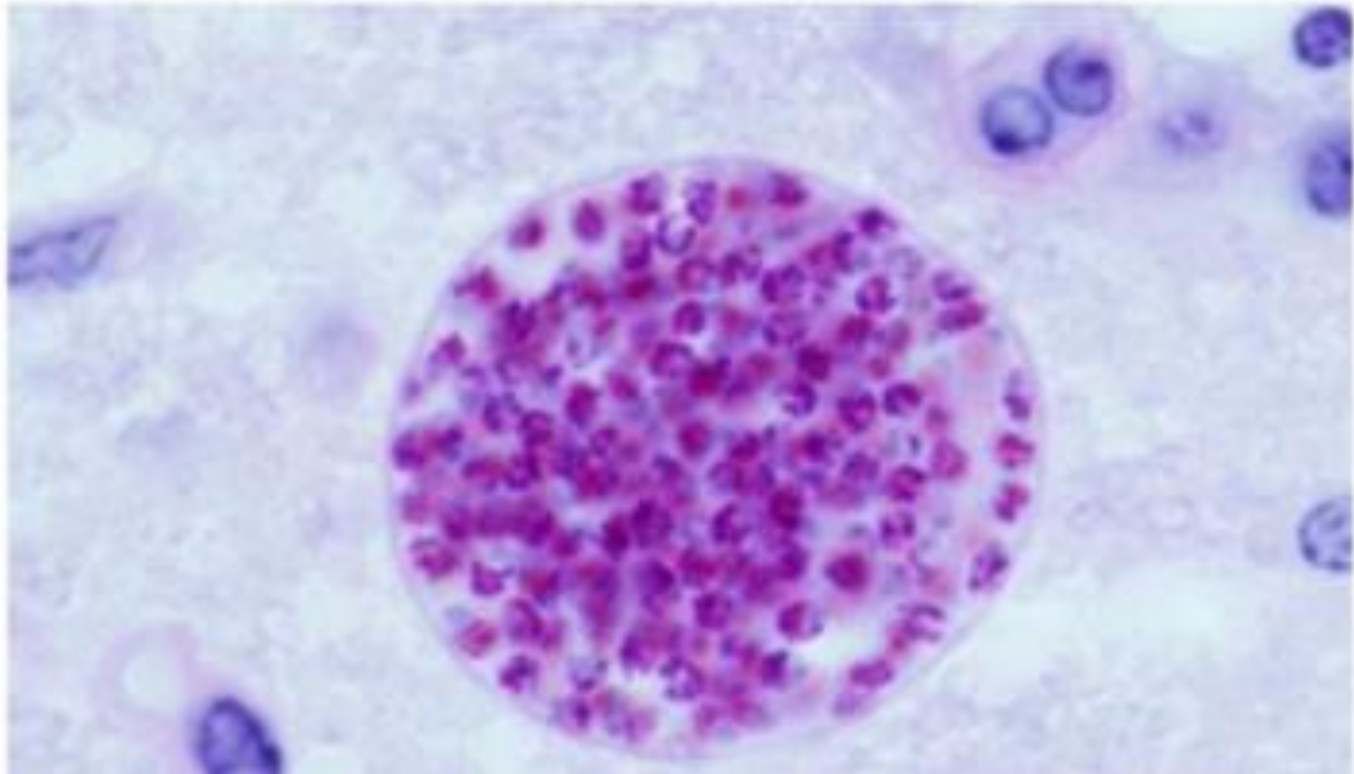


Tissue cyst (con)

- With **periodic acid Schiff (PAS)** stain, the cyst wall stains weakly, and the parasites inside are stained **deeply**. The **slowly multiplying parasites** within the cyst are called **bradyzoites**. The cyst is **round or oval**, **10–20 μm** in size and contains numerous bradyzoites. Cysts remain viable in tissue for several years

Tissue cyst

Image of a tissue cyst:



Oocyst

Oocysts develop only in **definitive hosts** – in the intestine of cats and other felines but not in humans,

It is **oval** in shape and measures **10–12 μm** in diameter . Each cyst is surrounded by a thick **resistant wall** . The oocysts is formed by sexual reproduction (**gametogony**). cats shed millions of oocysts per day in feces for about **2 weeks** during the primary infection. The freshly passed oocyst is not infectious . They undergo **sporulation** in the soil with formation of **2 sporocysts** , each containing **4 sporozoites**. The sporulated oocyst is infective.



OOCYST(CON)

- Oocyst is very resistant to environmental conditions and can remain infective in soil for about an **year**. When the infective oocyst is ingested, it releases **sporozoites** in the intestine, which initiates infection

Life Cycle

T. gondii completes its life cycle in 2 hosts.

Definitive host: Cats and other felines, in which both sexual and asexual cycle takes place.

Intermediate hosts: Man and other mammals, in which only the asexual cycle takes place.

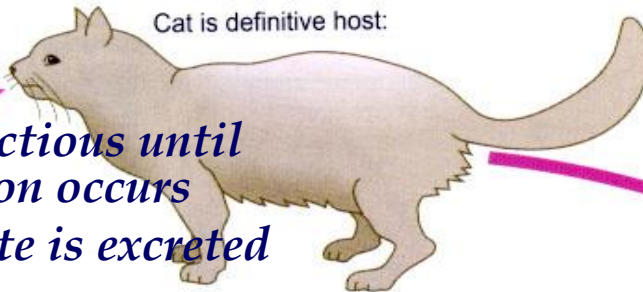
T. gondii has 2 types of life cycles:

☐ Enteric cycle

☐ Ex o-entric cycle.

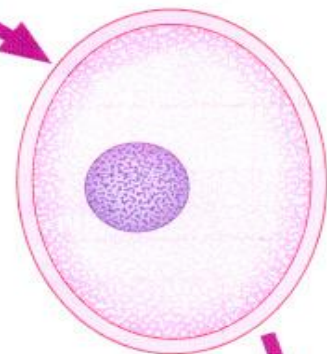
Cysts ingested by cat

Cat is definitive host:

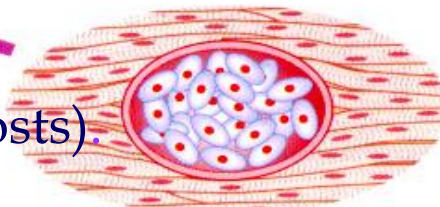


Unsporulated oocysts passed in faeces

Oocytes do not become infectious until they sporulate, sporulation occurs 1- 5 days after that the oocyte is excreted in the feces.



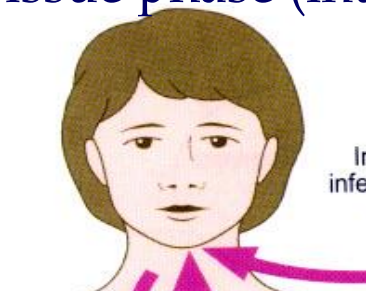
Tissue phase (intermediate hosts).



Cysts containing bradyzoites in tissues of intermediate host

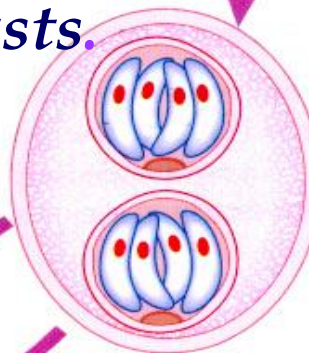
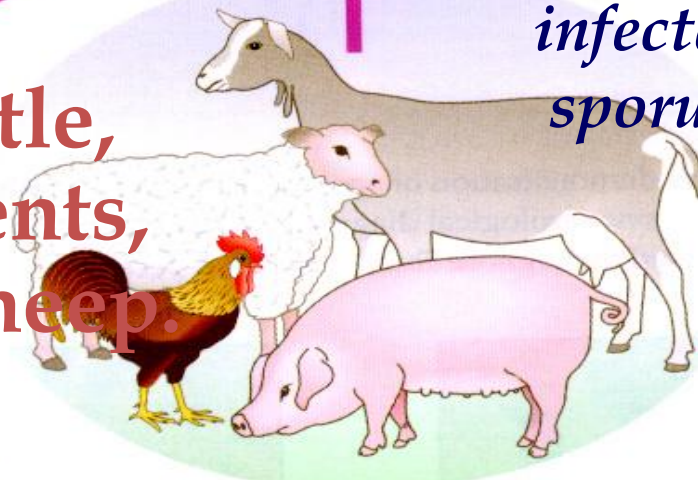
Intermediate host gets infected by ingesting sporulated oocysts.

Ingested cysts in infective meat (raw or undercooked)



Human, cattle, birds, rodents, pigs, and sheep.

Oocysts in feed, water, or soil ingested by intermediate host



Sporulated oocysts

Contaminated food and water

Intermediate host

Tachyzoites transmitted through placenta



Infected fetus

Enteric cycle

Enteric cycle occurs in cat and other **definitive hosts**. Both sexual reproduction (gametogony) and asexual reproduction (schizogony) occur within the **mucosal epithelial cells** of the small intestine of the cat. Cat acquires infection by ingestion of **tissue cysts** in the meat of rats and other animals or by ingestion of **oocysts** passed in its feces.

Enteric cycle (con)

- The **bradyzoites** are released in the small intestine and they undergo asexual multiplication (**schizogony**) leading to formation of **merozoites** . Some merozoites enter extra intestinal tissues resulting in the formation of **tissue cysts** in other organs of the Body.

INVASIVENESS

Extracellular

Intracellular

Gliding & Adhesion

Invasion

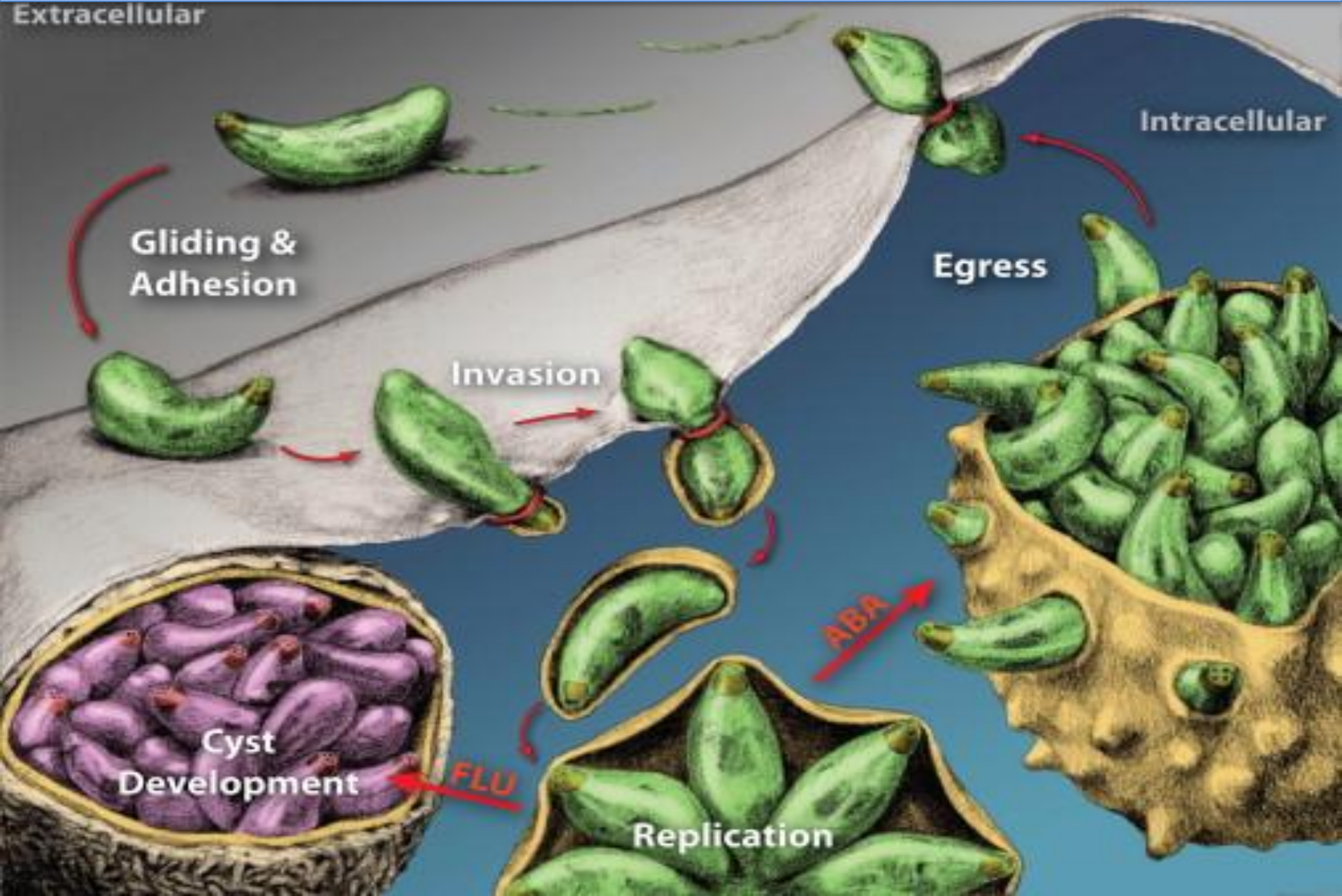
Egress

Cyst Development

Replication

ABA

FLU



Enteric cycle (con)

- Other **merozoites** transform into male and female gametocytes and **sexual cycle (gametogony)** begins , with the formation of **microgamete and macrogamete** . A macrogamete is fertilized by motile microgamete resulting in the formation of an **oocyst** , which passes through maturation stages (**sporulation**) in the soil after being excreted from host through feces.

Enteric cycle (con)

- A mature oocyst containing **8 sporozoites** is the **infective** form which may be ingested by rats or other mammals to repeat the cycle

Exo enteric cycle

- **Exo- enteric cycle** occurs in humans, mice, rats, sheep, cattle ,pigs and birds , which are the intermediate hosts .Humans acquire infection after:
 - Eating uncooked or undercooked infected meat , particularly lamb and pork containing tissue cysts
 - Ingestion of mature oocysts through food, water , or fingers contaminated with cat feces directly or
 - indirectly **via** Intrauterine infection from mother to fetus(**congenital toxoplasmosis**)

Exo entric cycle (con)

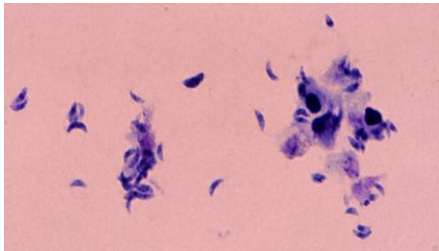
- D - [?] Blood transfusion E - transplantation from infected donors . **Sporozoites** from the oocysts and **bradyzoites from the tissue cysts** enter into the intestinal **mucosa and multiply asexually and tachyzoites** are formed (**endyogeny**). Tachyzoites continue to multiply and spread locally by lymphatic system

pathogenicity

- *Toxoplasma* infection depends on the **immune status** of the infected person . **Active progression of infection** is more likely in **immunocompromised** individuals. Toxoplasmosis has acquired great importance as one of the major **fatal complications** in **acquired immunodeficiency syndrome(AIDS)**. Most human infections are a symptomatic .Clinical toxoplasmosis may be **congenital or acquired**

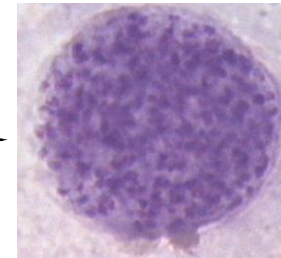
Toxoplasma gondii

ACUTE PHASE



Tachyzoites: rapidly dividing forms

CHRONIC PHASE



Bradyzoites: slowly dividing forms

Immunity +

Immunity -

ACTIVATION



Congenital toxoplasmosis

- **Congenital toxoplasmosis** : results when *T. gondii* is transmitted **transplacentally** from mother to fetus. This occurs when the mother gets primary toxoplasma infection, whether clinical or asymptomatic, during the pregnancy .**The risk of fetal infection rises with progress of gestation** ; from 25%, when the mother acquires primary infection in first trimester to 65% in the third trimester. the **severity of fetal damage is highest**, when infection is transmitted in early pregnancy.

Congenital Toxoplasmosis

1. **Intracerebral calcification.** toxoplasmic encephalitis
 2. **Hydrocephaly.**
 3. **Microcephaly .**
 4. **Convulsions.**
 5. **Mental retardation .**
 6. **Cardiomegaly .**
- } Congenital disease



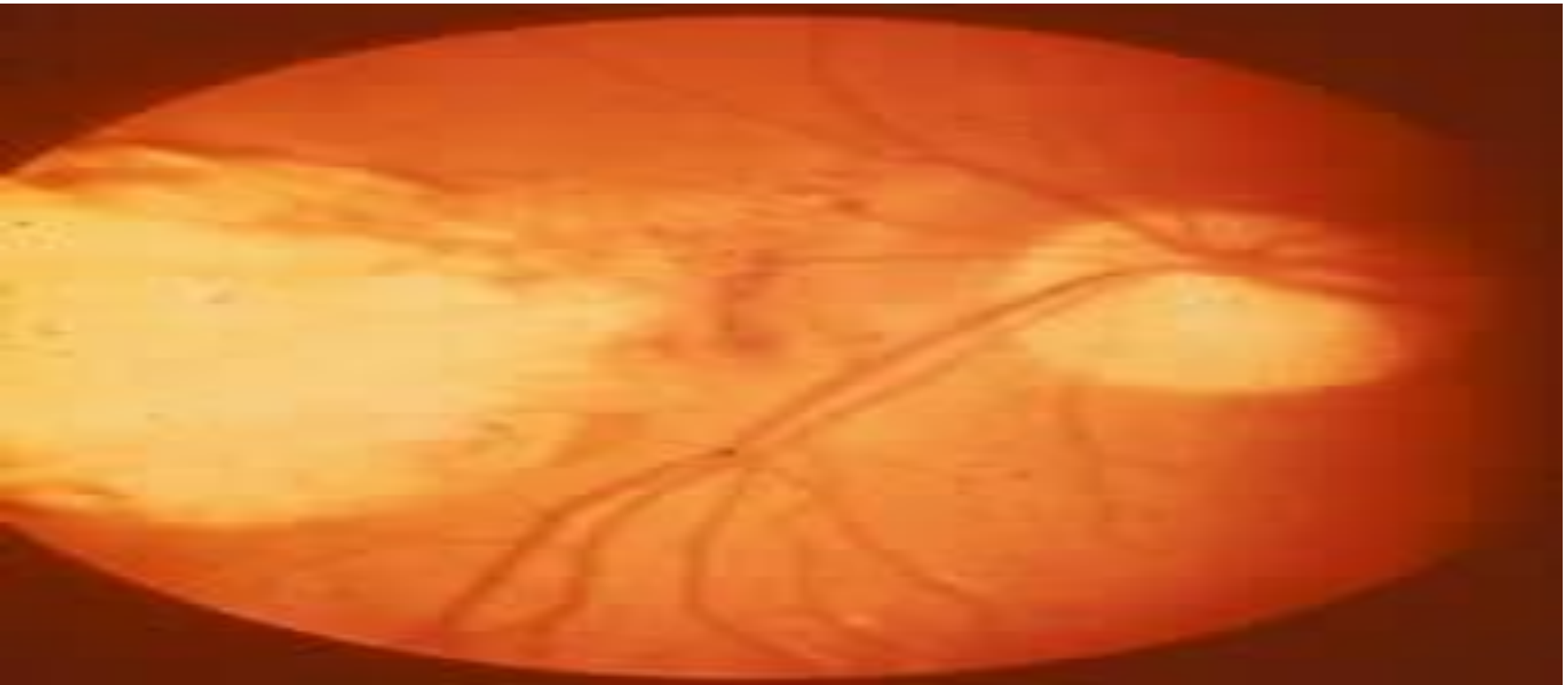
Acquired Toxoplasmosis

The most common manifestation of acute acquired toxoplasmosis is **lymphadenopathy**; the cervical lymph nodes being most frequently affected. **Fever, headache, myalgia, and splenomegaly** are often present. The illness may resemble **mild flu and is self limited**, although the **lymphadenopathy may persist**.

Ocular Toxoplasmosis

Another type of toxoplasmosis is ocular.

- It may present as uveitis, choroiditis, or chorioretinitis.



Severe, active retinochoroiditis

Laboratory diagnosis of *Toxoplasma gondii*

Microscopy

Tachyzoites and tissue cysts detected in blood, sputum and bone marrow aspirates

Stains used:

- Giemsa
- PAS
- GMS

Serodiagnosis

• Antibody detection:

Test for detecting IgG antibody:

- ELISA
- IFAT
- Latex agglutination test
- Sabin-Feldman dye test

Test for detecting IgM antibody:

- Double sandwich IgM ELISA
- IgM-ISAGA

Test for detecting IgA antibody:

- Double sandwich IgA ELISA

• Antigen detection:
by ELISA

Molecular diagnosis

- PCR

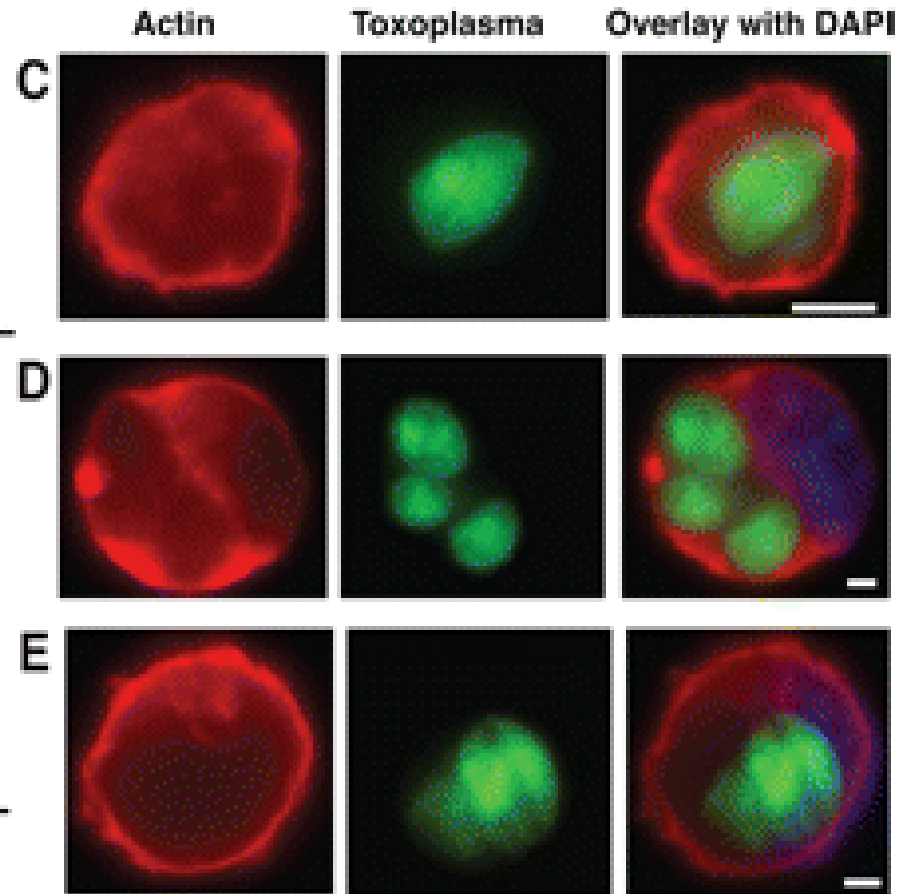
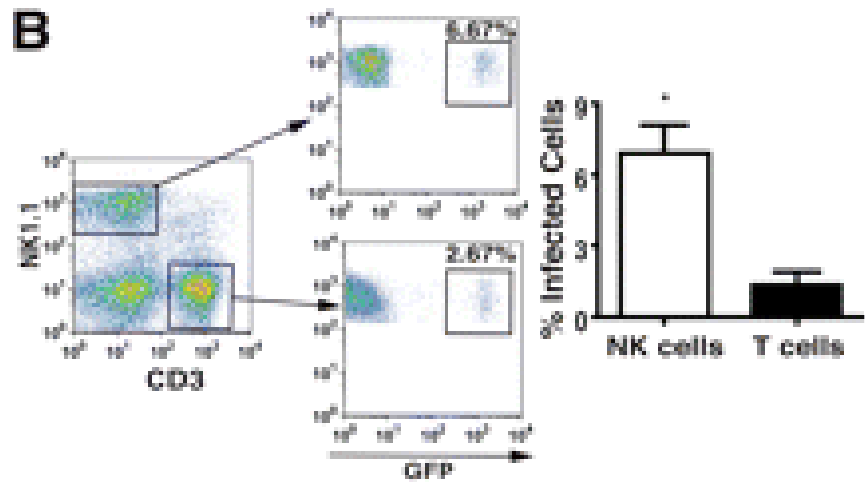
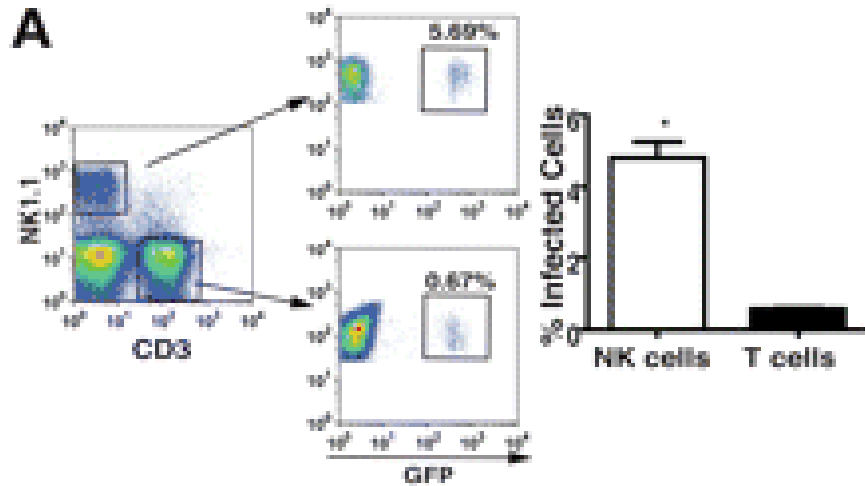
Imaging

- MRI and CT scan for central nervous system involvement
- USG for congenital toxoplasmosis

Others

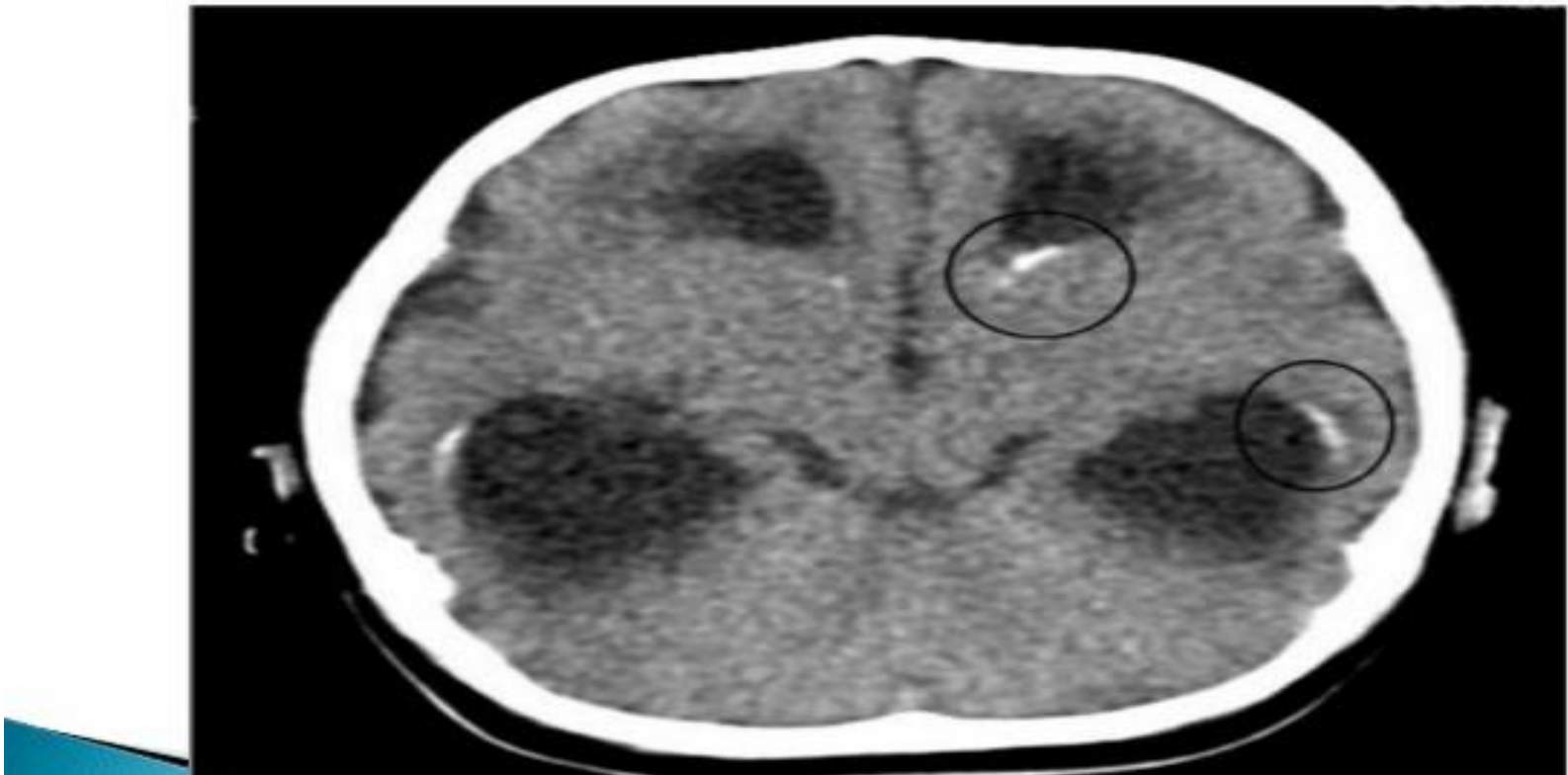
- Animal inoculation
- Skin test of frenkel

8-Flowcytometry

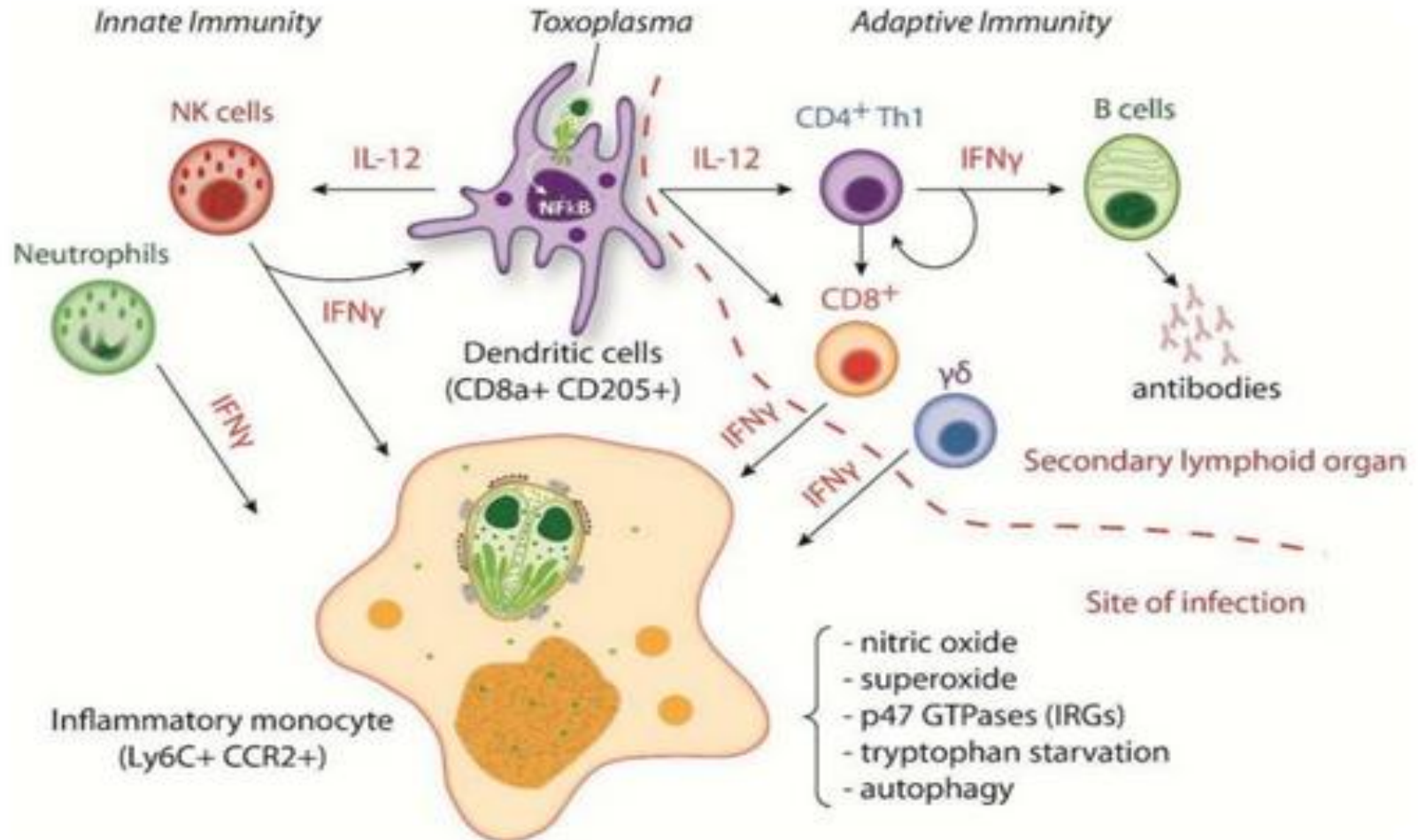


15-CT Image

CT image :

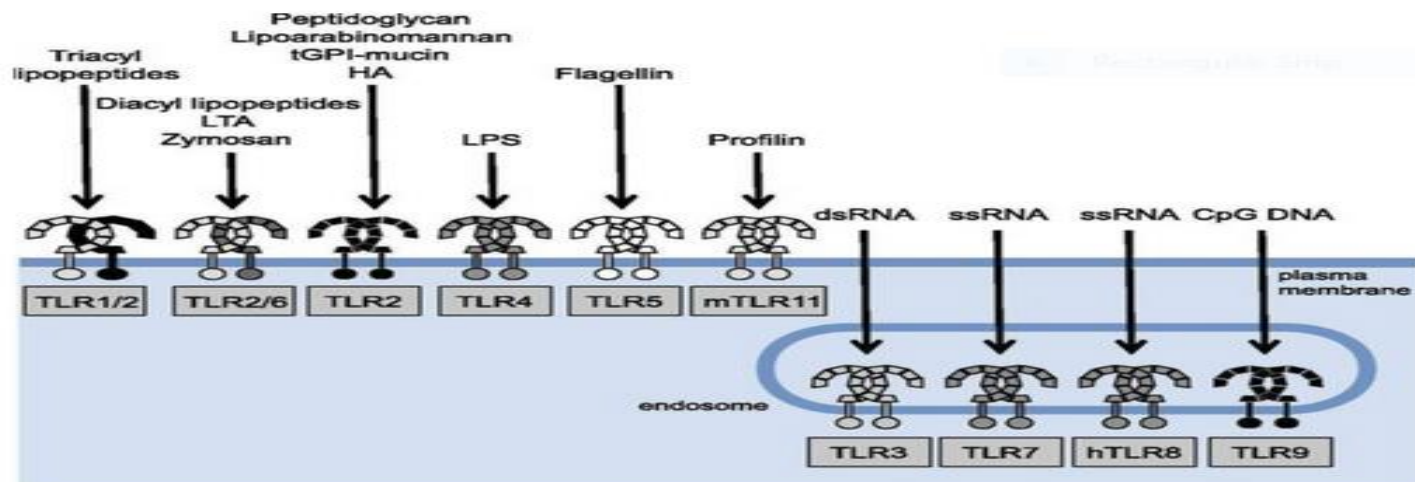


Immune Response to Toxoplasmosis



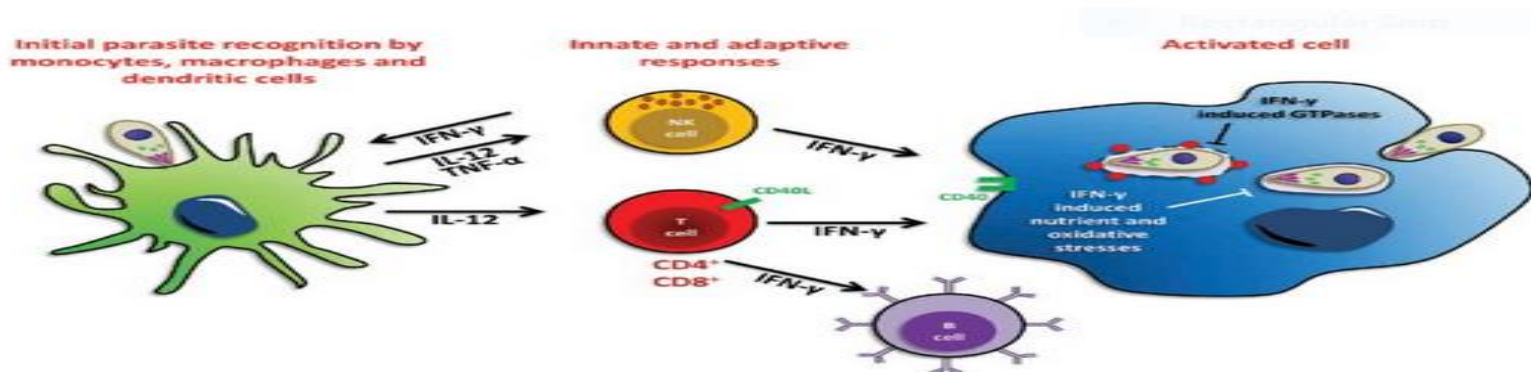
Recognition of T.gondii by Toll-like receptors (TLRs)

- Cell surface and intracellular Toll-like receptors (TLRs) and their ligands . TLRs are divided into two groups based on their cellular localization when sensing their respective ligands. TLRs 1, 2, 4-6, and 11 localize to the cell surface (cell surface TLRs) and TLRs 3 and 7-9 reside at endosomal compartments (intracellular TLRs). Cell surface TLRs respond to microbial membrane materials such as lipids, lipoproteins, and proteins, whereas intracellular TLRs recognize bacteria-and virus-derived nucleic acids.

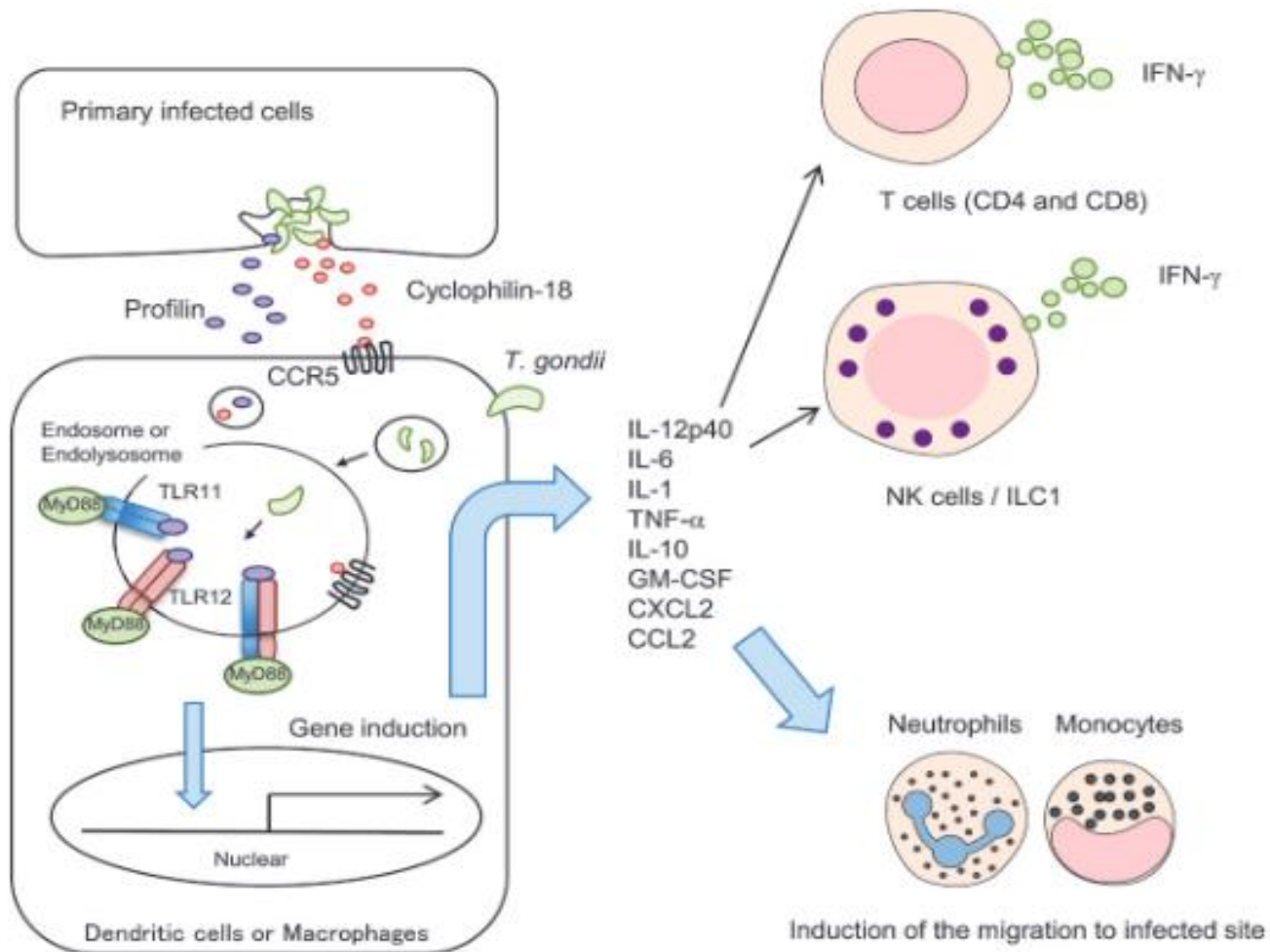


Immune Response to Toxoplasmosis

Initial host control of parasite infection induces the production of the pro-inflammatory cytokine interleukin 12 (IL-12) by macrophages and dendritic cells. IL-12 will in turn activate natural killer (NK) and T cells to secrete interferon γ (IFN- γ). Neutrophils and T cells also produce IFN- γ in response to infection. IFN- γ then activates several host defense mechanisms for intracellular elimination of *T. gondii*, including the activation of interferon-induced GTPases, and the induction of nutrient and oxidative stresses. Activated B cells can also help limiting the spread of the parasites to some extent.

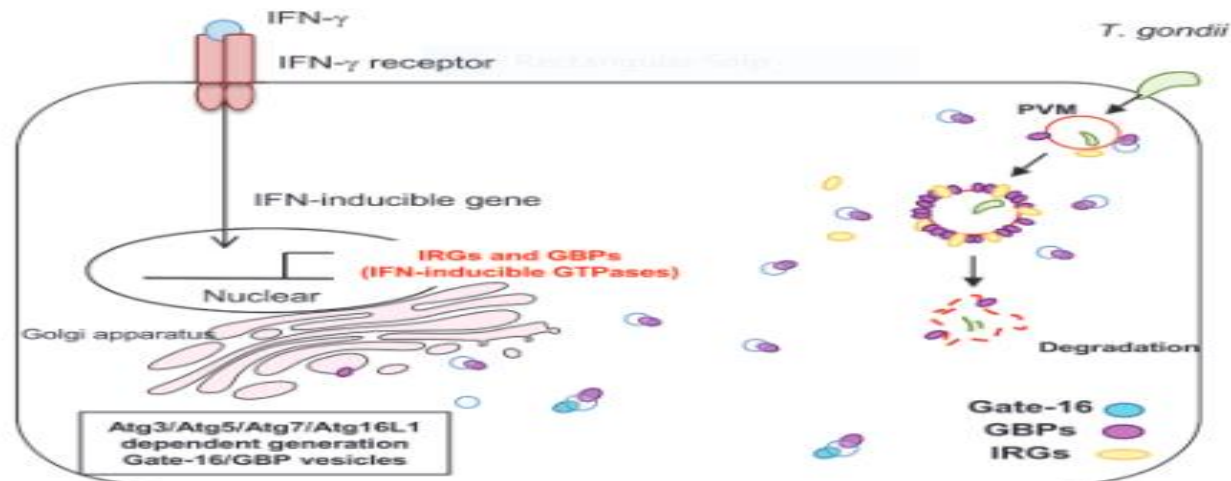


Immune Response to Toxoplasmosis(con)

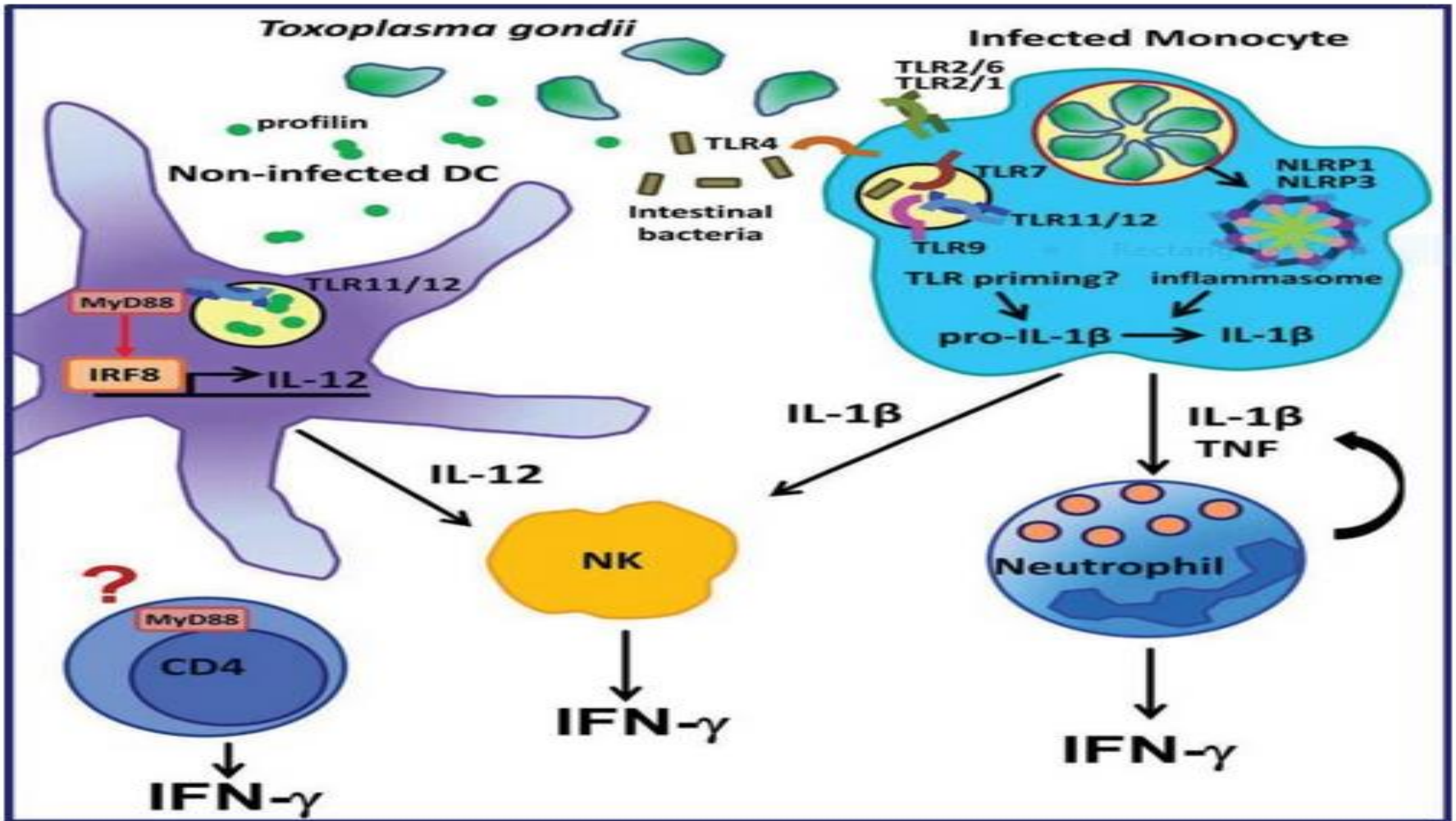


Cell-autonomous immune responses against *T. gondii* infection

- Most cells respond to IFN- γ stimulation by expressing several hundred genes, including four families of GTPases: MX proteins, p47 immunity-related GTPases (IRGs), VLIGs and p65 guanylate-binding proteins (GBPs). IRGs and GBPs are important for IFN- γ -induced anti-*T. gondii* responses

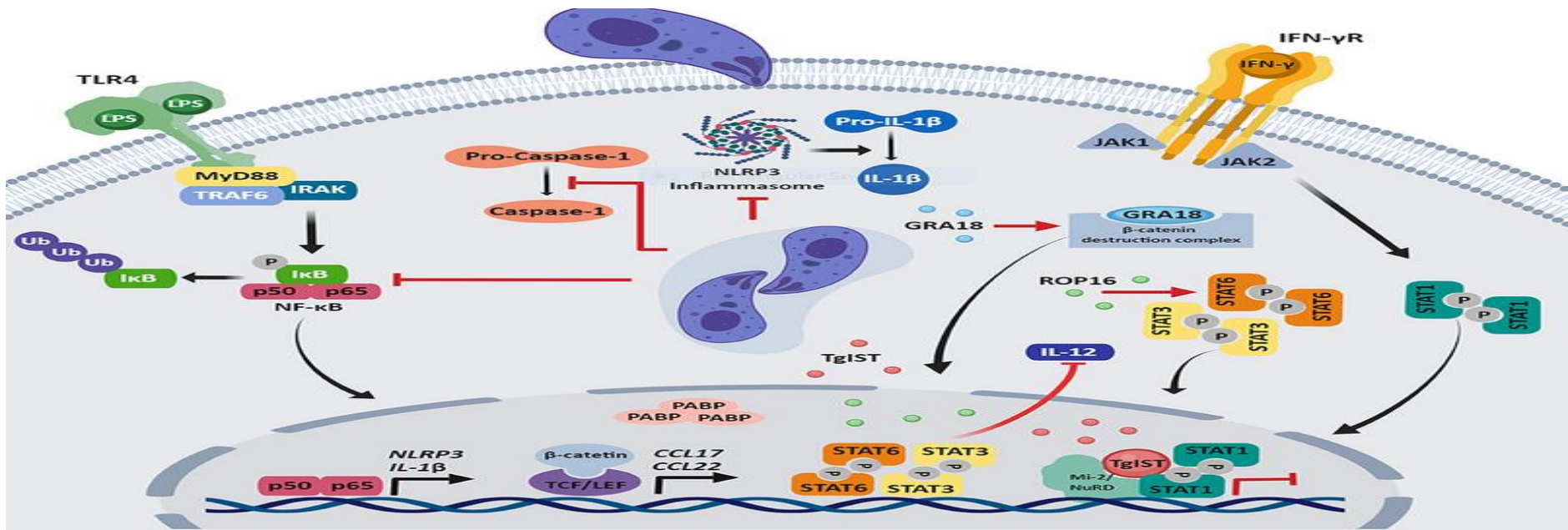


Evasion of Immune Response



1 - Modulation of host immune signaling by *T. gondii*. After invasion of the host cells

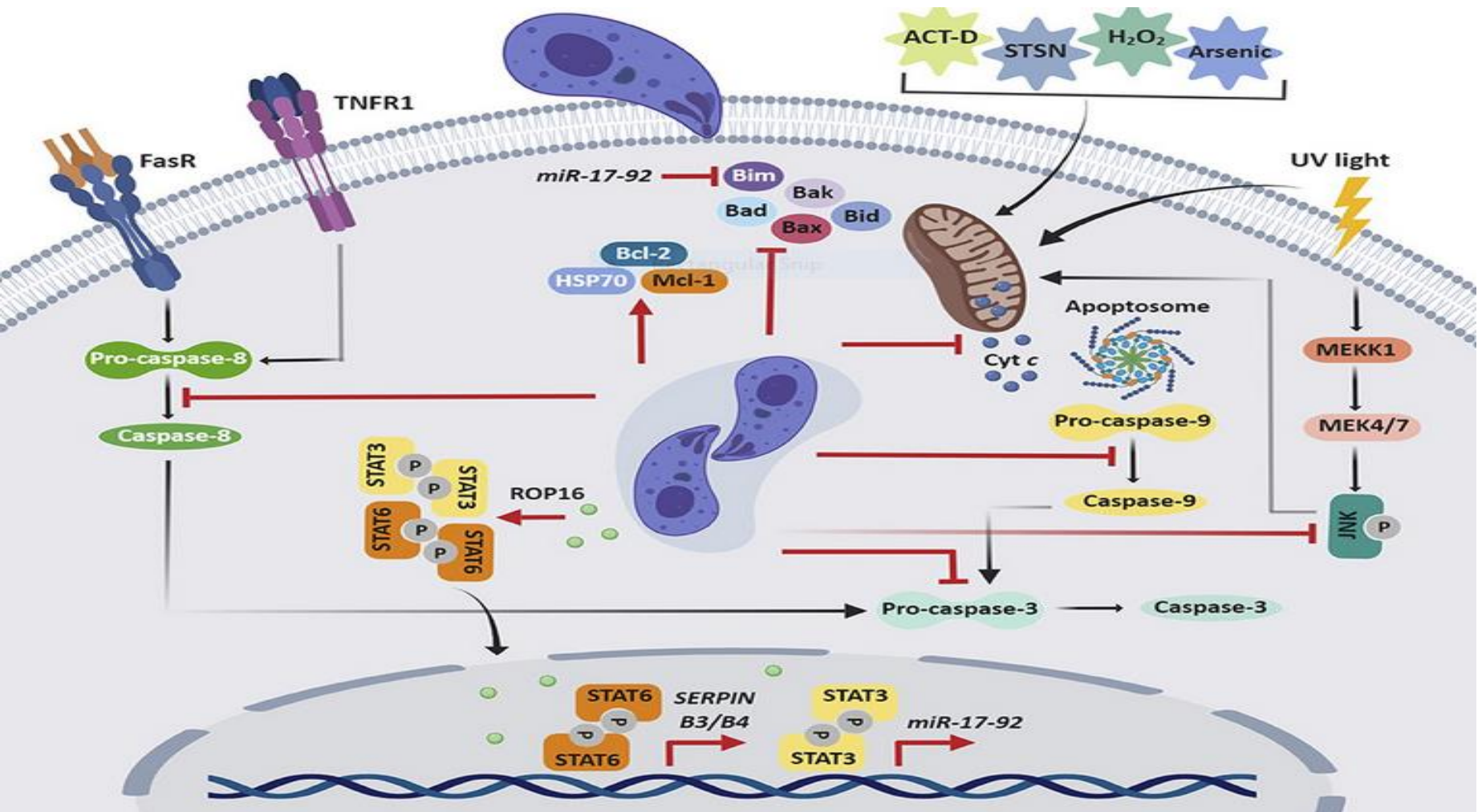
- Parasite effector proteins that govern many of these host-pathogen interactions are secreted from the apical secretory organelles and are found in the host cytosol, associate with the PVM, or translocate to the host nucleus. *T. gondii* inhibits the expression of IFN- γ responsive genes by preventing the dissociation of STAT1 from DNA, hampering its recycling and further cycles of STAT1-mediated transcription



2 - *T. gondii* inhibition of host cell apoptosis

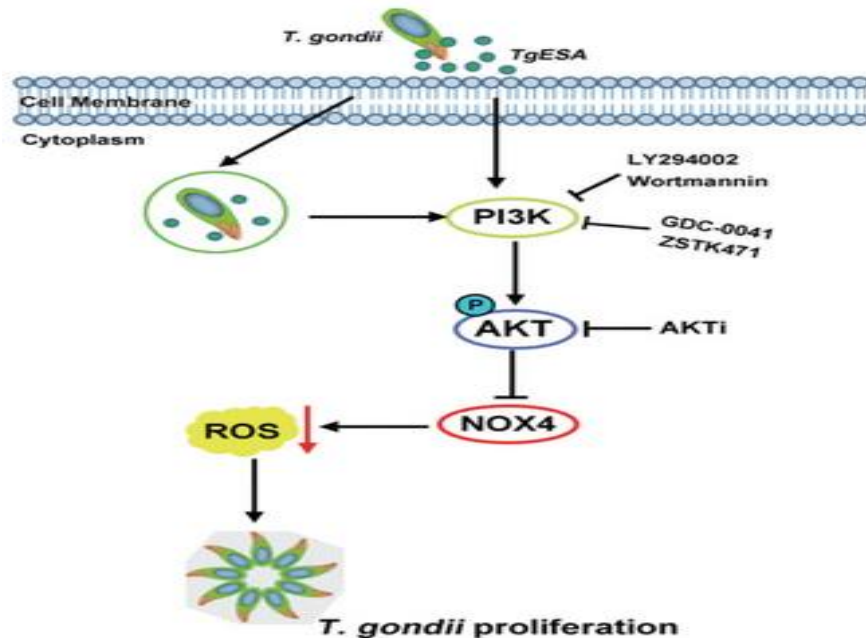
- *T. gondii* impairs both cell-intrinsic (mitochondrial) and -extrinsic (death receptor-mediated) pathways of apoptosis, which allows the parasite to maintain its replicative niche. *T. gondii* can interfere with the initiation, activation, or signaling of the apoptotic cascade, which may result from an indirect mechanism or the direct effect of secreted parasite effector proteins. ACT-D, actinomycin D; STSN, staurosporine; Cyt c, cytochrome c.

2 - *T. gondii* inhibition of host cell apoptosis (con)



3-Evading Intracellular Death

- *T. gondii* targets the main NADPH oxidase by reducing Nox4 at the transcript and protein levels, resulting in decreased intracellular ROS. The effect on Nox4 expression was associated with activation of PI3K/AKT signaling in infected cells





THANK YOU FOR LISTEN