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Investigation of infectivity of neonates and adults from different rat strains to *Toxoplasma gondii* Prugniaud shows both variation which correlates with iNOS and Arginase-1 activity and increased susceptibility of neonates to infection

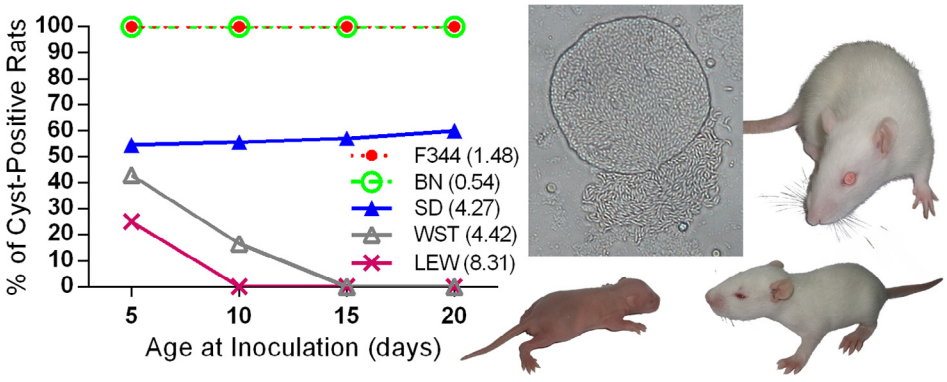
Jiang-Mei Gao [a], Si-Qi Yi [a], Ming-Shui Wu [a], Guo-Qing Geng [a], Ji-Long Shen [b], Fang-Li Lu [c], Geoff Hide [d], De-Hua Lai [a,*], Zhao-Rong Lun [a,d,**]

[a] *Center for Parasitic Organisms, State Key Laboratory of Biocontrol, School of Life Sciences, Key Laboratory of Tropical Disease Control of the Ministry of Education, Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou 510275, China*
[b] *The Anhui Provincial Laboratory of Pathogen Biology, Anhui Medical University, Hefei 230032, China*
[c] *Department of Parasitology, Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou 510080, China*
[d] *Ecosystems and Environment Research Centre and Biomedical Research Centre, School of Environment and Life Sciences, University of Salford, Salford M5 4WT, UK*

HIGHLIGHTS

- Different strains of rat show variation in resistance to *T. gondii* infection.
- The balance of iNOS/Arginase-1 activity of host is strongly linked to resistance.
- The rat is a good model for understanding toxoplasmosis in humans.
- Neonates of rat already show similar resistance to *Toxoplasma* infection as adults.

GRAPHICAL ABSTRACT



* Corresponding author. Fax: +86-20-84036215.
E-mail address: laidehua@mail.sysu.edu.cn (D-H. Lai).
** Corresponding author. Fax: +86-20-84036215.
E-mail address: lsslzr@mail.sysu.edu.cn (Z-R. Lun).

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ABSTRACT

Mouse models differ considerably from humans with regard to clinical symptoms of toxoplasmosis caused by *Toxoplasma gondii* and, by comparison, the rat model is more representative of this disease in humans. In the present study, we found that different strains of adult and newborn rats (Lewis, Wistar, Sprague Dawley, Brown Norway and Fischer 344) exhibited remarkable variation in the number of brain cysts following inoculation with the *T. gondii* Prugniaud strain. In adult rats, large numbers of cysts (1231 ± 165.6) were observed in Fischer 344, but none in the other four. This situation was different in newborn rats aged from 5 to 20 days old. All Fischer 344 and Brown Norway newborns were cyst-positive while cyst-positive infection in Sprague Dawley neonates ranged from 54.5% to 60% depending on their age at infection. In Wistar and Lewis rat neonates, however, cyst-positivity rates of 0–42.9% and 0–25% were found respectively. To investigate whether rat strain differences in infectivity could be related to inherent strain and genetic differences in the host immune response, we correlated our data with previously reported strain differences in iNOS/Arginase ratio in adult rats and found them to be linked. These results show that interactions between host genetic background and age of rat influence *T. gondii* infection.

1. Introduction

Toxoplasma gondii is an obligatory intracellular apicomplexan parasite that infects almost all warm-blooded vertebrates, including mammals and birds. It is considered that *T. gondii* is one of the most successful eukaryotic pathogens based on the wide range of host species and high prevalence in these species worldwide. Human infections with *T. gondii* are primarily caused by ingesting undercooked meat containing viable tissue cysts or by ingestion of food or water contaminated with oocysts in faces shed from infected cats. It is widely reported that up to one-third of the world's population are estimated to be chronically infected (Dubey, 2004; Dubey and Beattie, 1988) and pregnant women are highly at risk in endemic areas due to the cause of congenital birth defects by toxoplasmosis (Gao et al., 2012; Pappas et al., 2009).

Acute parasitic infection with *T. gondii* is usually not found in immunocompetent individual humans, who can mount an effective immune response to clear most tachyzoites but not bradyzoites which remain in tissue cysts. Cysts of *T. gondii* can develop in varied organs and tissues, particularly in the brain or skeletal muscles, which can later be reactivated if immunosuppression (e.g. AIDS, cancer therapy or organ transplantation) occurs. This reactivation of latent infection can cause life-threatening toxoplasmic encephalitis and related diseases (Dubey et al., 2006; Gianotti et al., 1997; Supiot et al., 1997). Increasingly evidence indicates that *T. gondii* infection is strongly linked to serious recurrent ocular disease in some regions of Southern Brazil (Dubey et al., 2012; Jones et al., 2006) and to a risk of schizophrenia (Torrey and Yolken, 2003; Torrey et al., 2007).

Infection by *T. gondii* differs profoundly between species (Sepulveda-Arias et al., 2008). There is evidence that not only the immune status, but also the genetic predisposition of the hosts influence the clinical outcome of *T. gondii* infection (Kempf et al., 1999). Mice, for instance, are susceptible to *T. gondii* infection. All strains of mouse, as far as we know, die from the infection by the virulent type I strains e.g. the RH strain of *T. gondii* (Sibley and Boothroyd, 1992). However, they can also develop chronic infections if they are inoculated with low doses of the less virulent type II strains such as the Prugniaud and ME49 strains or the type III strains such as the VEG strain (Saeij et al., 2005).

For many reasons, the majority of our knowledge on the genetic and immunological mechanisms involved in the control of *T. gondii* infection has been obtained by using mouse models, in which, the genetic background, the inoculation route, the inoculum size, the age and the sex of the host may all influence the outcome of infection (Dubey, 1987; Johnson et al., 1995; Liesenfeld et al., 2001; Walker et al., 1997). Unfortunately, however, data from the mouse model may not actually mirror the processes involved in human toxoplasmosis since the pathogenesis and the susceptibility in mice are remarkably different from that observed in humans (Kempf et al., 1999).

In contrast, many studies have demonstrated that adult rats are one of the most resistant hosts to *T. gondii* infection with respect to clinical toxoplasmosis and this phenomenon has been known for more than half a century (Benedetto et al., 1996; Evans et al., 2014; Fujii et al., 1983; Lewis and Markell, 1958; Li et al., 2012; Nakayama and Hoshiai, 1960). The similarity between the clinical course in rat and human toxoplasmosis suggests the use of rats as an ideal model to elucidate the mechanism of *Toxoplasma* infection in humans (Darcy and Zenner, 1993; Santoro et al., 1987; Zenner et al., 1998, 1999a, 1999b).

Pioneering work showed that different strains of rat exhibited considerable variation in the brain cyst load following inoculation. For example, the Lewis rat was shown to be highly resistant to cyst formation; in contrast however, Fischer 344 and Brown Norway rats are more susceptible (Kempf et al., 1999; Sergent et al., 2005). Interestingly, Guerrero et al. (1995) found that different age groups of Sprague Dawley rats also presented variance in resistance to *T. gondii* infection.

More recently, previous studies (Li et al., 2012) showed that, when comparing resistant and susceptible hosts with *T. gondii* (virulent RH strain) infection, high iNOS and low Arginase levels were correlated with resistant hosts (rats) and high Arginase and low iNOS levels were correlated with sensitive hosts (mice). Furthermore, that study showed that, between the rat inbred lines, there was variation in both resistance to *T. gondii* (RH Strain) and ratios of iNOS/Arginase in the five rat strains studied.

These findings are intriguing, but these older studies (Guerrero et al., 1995; Kempf et al., 1999; Sergent et al., 2005) concentrate on using a small number of rat strains and there are very little comparative data on neonatal infection in the same strains. Consequently, it is difficult to make comparisons between adult strains and neonatal infection within the same strains. Furthermore, the more recent studies (Li et al., 2012) concentrate on infection using the virulent (non-cyst forming) *T. gondii* strain which may not be typical in natural infections. In order to build up a systematic view of a rat model for understanding the human toxoplasmosis, the aims of our present study are focused on the resistance/susceptibility to the cyst-forming Prugniaud strain of *T. gondii* infection in newborns and adults of five rat strains. We aim to investigate whether the differences in resistance/susceptibility are related to innate genetic mechanisms within the host immune response and specifically to investigate any correlations, in adult rats, with the previously reported iNOS/Arginase ratios (Li et al., 2012) for those five inbred lines. The impact of the results from this work may provide very useful data to help to gain a better understanding of human toxoplasmosis.