ANIMAL MODELS OF LEISHMANIASIS: A REVIEW

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INTRODUCTION

Leishmaniasis is a disease caused by the protozoan parasites belonging to the genus Leishmania. The disease is included in the list of the world’s most neglected diseases, prevalent in developing countries (McCall et al., 2013). It ranks the second only to malaria, and the control remains a serious problem with ever increasing cases worldwide (WHO, 2002). Leishmania infection continues to have a major impact on public health inducing significant morbidity and mortality mostly in the poorest populations (Badlee et al., 2013). The world’s leishmaniasis prevalence is between 1.5 to 2.5 million cases each year (Singh et al., 2006) and a further, more than 350 million people are living at risk in 98 countries (WHO, 2010). The transmission of leishmaniasis occurs through vectors of genus Phlebotomous in Old World and Lutzomyia in the New World (Weniger et al., 2001).

A. Mouse model

Outbred mice are generally resistant to infection with L. donovani (visceral leishmaniasis) but inbred strains of mice are widely used with susceptible, resistant and intermediate strains that share similarities with human visceral leishmaniasis. There is a generic basis for susceptibility to infection with L. donovani based on the presence of Scl11a1 gene (Blackwell, 1996; Liew and O’Donnell, 1993). The Scl11a1 gene encodes a protein expressed on the membrane of infected phagosomes that removes Fe2+ Mn2+ ions from the intra-phagosomal compartment restricting intracellular Leishmania multiplication in iron-limited intracellular environments (Huynh and Andrews, 2008; Marquis and Gros, 2007). Genetically resistant mouse strains (e.g., CBA) possess a functional Scl11a1 gene which confers innate resistance to early Leishmania parasite growth. In contrast, susceptible mice strains (e.g., C57BL/6 and BALB/c) possess a non-functional Scl11a1 gene and early parasite growth in the liver cannot be controlled (Kaye et al., 2004). However, most susceptible mouse strains, including BALB/c, develop acquired immune mechanisms to control hepatic parasite growth at later stages of infection (Stanley and Engwerda, 2007).

B. Hamster model

Although many hamster species are susceptible to L. donovani infection, the Syrian golden hamster (Mesocricetus auratus) establishes a good model for VL and provides a more synchronous infection in liver and spleen that can develop into chronic infection more similar to human VL (Hommel et al., 1995). The usual routes of infection in the hamster model of VL are intracardiac and intraperitoneal. However, the administration of parasites by the saphenous vein in order to minimize stress on the hamsters has also been reported (Lei et al., 2001).
In this model, surprisingly, there are significant amounts of Th1 cytokines (IFN-γ, IL-2 and TNF-α) in the spleen, but there is little or no IL-4. However, to allow the parasites to multiply, deactivating Th2 cytokines (TGFBeta and IL-10) may act on infected macrophages as well as anti-Leishmanial antibodies (which have no protective role in leishmaniasis) that opsonize amastigotes and induce IL-10 production in macrophages. These high activation and deactivation processes are likely to occur mainly in the spleen and liver (Goto and Prianti, 2009). Interestingly, Syrian hamsters exhibit reduced expression of the gene encoding iNOS in response to IFN-γ, and this is thought to lead to a low NO generation, subsequently defaulting in parasite killing (Goto and Lindoso, 2004). Thus Syrian hamster is a suitable experimental model for the study of the pathological features of active VL, but it is not a suitable model for the evaluation of immunization strategies, as a result of the animal’s high innate susceptibility. In Syrian hamsters, manifestations of VL can range from asymptomatic and oligosymptomatic infections to progressive fatal visceral disease (Melby et al., 2001). The pathological features reported during VL include hypoplasia of the white pulp in the spleen, hepatic granulomas and the deposition of a secondary amyloid substance both in the spleen and the liver (Rica-Capela et al., 2003). Also, other studies of active VL have reported that infected hamsters develop glomerulonephritis associated with deposition of immunoglobulins and parasite antigens (immune complexes) in the kidneys. Finally, the disseminated amyloidosis and glomerulonephritis produce renal failure and nephritic syndrome in infected hamsters (Sartori et al., 1992). The visceral infection in hamsters also induces pathological alterations in hepatocytes, mainly in the endomembrane system and the peroxisomal compartment, leading to a disturbance of liver metabolism (Vianna et al., 2002).

C. Dog model

Dogs have also been used as experimental models of Leishmania infections and experimental infections have been achieved with Leishmania spp. for which it is not a natural reservoir e.g. L. donovani from India (Chapman et al., 1979). German shepherd dogs are reported to give better results than beagles but some workers claim high successful infection rate with mixed breeds (Abranches et al., 1991).

D. Non Human primate model

Monkeys are normally the experimental animals to be used in studies of the efficacy and safety of vaccines and drugs. Earlier studies in establishing VL in New and Old World monkeys demonstrated that Alouatta trivirgatus (owl monkeys) (Chapman et al., 1983) and Saimiri sciureus (squirrel monkey) (Chapman and Hanson, 1981) developed an acute and fulminating, but short lived, infection. Old World monkeys such as Macaca spp. viz. M. mulatta, M. fascicularis and M. nemestrina, and African vervet monkeys developed low and/or inconsistent infections (Hommel et al., 1995). The infected animals presented all the clinicoinmunopathological features as observed in human kala azar (Anuradha et al., 1992; Dube et al., 1999). The Indian langur has also been used for preclinical evaluation of potential antileishmanial drugs and vaccines (Dube et al., 1998; Misra et al., 2001).

References


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