GENETIC FACTORS CONFERRING SENSITIVITY OR RESISTANCE TO LEISHMANIOSIS: COMPARATIVE ASSESSMENT IN ANIMALS AND HUMANS

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John Ikonomopoulos
Laboratory of Anatomy and Physiology of Farm Animals, Department of Biosciences, Faculty of Animal Science and Aquaculture, Agricultural University of Athens, Greece
ikonomop@aua.gr

Antonia Mataragka
Laboratory of Anatomy and Physiology of Farm Animals, Department of Biosciences, Faculty of Animal Science and Aquaculture, Agricultural University of Athens, Greece

Abstract

Leishmaniosis is a zoonotic disease, which is very common in many parts of the world, and is caused by protozoa of the genus Leishmania that act as obligatory intracellular parasites of humans and animals. The investigation of genetic predisposition to infectious diseases has resulted in significant discoveries in connection with the specific disease, in both humans and animals. These discoveries are reviewed in this article, in order to improve understanding of the pathogenesis of leishmaniosis and facilitate their integration in veterinary practice. The main immune mechanisms that affect the development of the infection induced by Leishmania are two, and though closely interacting, can be viewed for analytical purposes as distinct. The first of these mechanisms is the inherent ability of macrophages to contain the spread of the specific pathogen, after the infection has been established, and the second, the selective activation of Th1 and Th2 lymphocytes, leading to protection from, or exacerbation of the disease, respectively. The genetic foundation of the specific mechanisms is very complex, but it seems that the genes primarily involved in their control are the following: Nos2, NRAMP1, MHC, NOD2, Scl1, CBD1 και Scl2. Based on the activity of these genes and their interaction with cytokines, it is deducted that targeted administration of the latter to patients with leishmaniosis can redirect immune response towards improving the control of the infection, thus preventing heavy clinical disease. In conclusion, the study of the genetic predisposition of humans and animals to leishmaniosis is necessary in clarifying its pathogenesis, and can improve diagnostic and clinical management of patients to the benefit of public and animal health.

Keywords: *leishmaniosis, genetic predisposition, acquired immunity*

Introduction

Leishmaniosis is a very common zoonotic disease in many parts of the world, and is caused by protozoa of the genus *Leishmania* that act as obligatory intracellular parasites of humans and animals (Theodoropoulos and Theis, 1989), (WHO, 2018). More than one billion people around the world are exposed annually to the specific disease, which leads to 700,000-1,000,000 new cases per year, 3-5% of which are fatal (WHO, 2018).

Recent evidences of disease surveillance indicate significant increase in the prevalence of leishmaniosis due to the spread of AIDS in many parts of the world, including Europe (Desieux and Alvar 2003), (Gramiccia et al., 2005). Indicative of the alarming epidemiological association between leishmaniosis and AIDS is that both diseases have already become endemic in 35 countries (WHO, 2018).

The investigation of genetic predisposition to infectious and autoimmune diseases has resulted in significant discoveries in connection with many of them, including tuberculosis, brucellosis, sarcoidosis, Crohn's disease, asthma, and many forms of cancer (Searle and Blackwell 1999), (Sanjeevi et al., 2000), (Paccagnini et al., 2009), (Gregersen and Olsson, 2010), (Pradhan et al., 2010), (Goris and Liston, 2012). The relevant evidences with regards to leishmaniosis of humans and animals are reviewed in this article, in order to improve understanding of disease pathogenesis, and facilitate their integration in veterinary practice.

Genetic constitution and immune response

The immune mechanisms that primarily affect the development and outcome of the infection induced by *Leishmania* are two, and though closely interacting, can be viewed for analytical purposes as distinct. The first of these mechanisms is the inherent ability of macrophages to contain the spread of the specific pathogen, after the infection has been established (Green et al., 1990), and the second, the selective activation of *Th1* and *Th2* lymphocytes, leading to protection from, or exacerbation of the disease, respectively (Gumy et al., 2006).

Of key-significance in controlling macrophage phagocytic ability is the *nitric oxide synthese 2* gene (*Nos2*). Activation of *Nos2* promotes synthesis of nitric oxide, which increases acidification of the phagolysosome, improving phagocytic ability of macrophages and containment of the infection (Diaz et al., 2003), (Stager et al., 2003), (Baneth et al., 2008). This mechanism strongly influences genetic predisposition to infections induced, not only by leishmania, but every intracellular pathogen, at individual and species level. The latter is probably associated with the fact that predisposition to leishmaniosis is more pronounced in specific breeds of dogs, including the Boxer, Doberman, German Shepherd and Cocker Spaniel (Abranches et al., 1991), (França-Silva et al., 2003), (Sanchez-Robert et al., 2005).

Selective activation of *Th1* and *Th2* lymphocytes is determined through the combined activity of several genes and cytokines (Fondevila 1997), (Gumy et al., 2006), (El-Safi et al., 2006). In more detail, *Th1* activation is associated with resistance to leishmaniosis and relies on a two-way interaction between the latter type of lymphocytes and interferon-gamma (IFN-γ), tumor necrosis factor (TNF), and interleukins 2 and 12 (IL2, IL12), (De Lima et al., 2007), (Cecílio et al., 2014). Animals with stronger *Th1* response may present transient increase in antibody titre or become carriers of leishmania, but will not develop heavy clinical disease; these animals will also respond better to treatment and with less chances of relapse (Barbiéri, 2006), (Tripathy et al., 2006), (Gradoni, 2015), (Srivastava et al., 2016). It is noteworthy that in humans, the genes associated with *Th1* immune response have been linked with sensitivity or resistance, not only to leishmaniosis, but also tuberculosis, brucellosis, leprosy, asthma and various forms of cancer (Vidal et al., 1993), (Nylén and Gautam, 2010), (Kochi, 2016).

B-lymphocyte proliferation is much stronger in individuals that develop predominantly a *Th2* immune response, which is associated with the activity of IL4, IL5, IL6 and IL10, and results in increased production of antibodies. Passive trapping of the immune complexes

formed by the anti-leishmania antibody in basal membranes of glomerular cells may lead to proteinuria, loss of weight, renal failure and rapid clinical deterioration (Chakour et al., 2003), (Stager et al., 2003), (Ansari et al., 2006). Cellular immunity in the specific individuals is impaired, which is documented by the decrease in lymphocyte replication, following *in vitro* exposure to *Leishmania* antigens (Pinelli et al., 1994), (Bourdoiseau et al., 1997).

The outcome of the infection seems to be so clearly associated with the prevailing type of *Th* immune response that even after *Th2* activation, blocking IL-2 during the first stages of infection triggers *Th1* stimulation. The latter finding has been recorded as a consequence of the immune response evoked against *Leishmania major* (Gumy et al., 2006), and indicates that irrespective to genetic predisposition, the immune reaction associated with disease resistance can be influenced and possibly selectively directed by external factors.

The fundamental significance of the balance between Th1 and Th2 immune response is further documented by the response of humans to treatment inductive of cytokine activation associated with Th1 stimulation, such as IFN-γ and IL-12. The exact opposite event, i.e. sensitivity to leishmaniosis, has been recorded in response to increased concentration of cytokines that evoke a Th2 immune response, such as IL-10 (WHO, 2010). Thereof, it should be considered probable that the immune deficiency recorded in patients with visceral leishmaniosis is linked to the proliferation of CD4+ and CD25+ lymphocytes. Notably, the population of the specific classes of lymphocytes is adversely affected by treatment, which when administered in the early stages of leishmaniosis, results in significant decrease and improved clinical development (WHO, 2010).

Genes affecting the outcome of infection

The genes that affect or determine sensitivity to the infection induced in humans and animals by leishmania, and their activity are outlined below:

A) The gene coding the natural resistance macrophage protein 1 (*NRAMP1*).

NRAMP1 that is currently referred to as *solute carrier family 11 member 1* (*Slc11α1*), is located in the mouse and human chromosome 1 and 2p35, respectively (Vidal et al., 1993). The specific gene was the first to be recognized as responsible for formulating, and not simply influencing, resistance or sensitivity to leishmaniosis, something which has been demonstrated too, in connection with toxoplasmosis, tuberculosis, brucellosis, salmonellosis, asthma and rheumatoid arthritis (Blackwell et al., 2003). The NRAMP1/SLC11A1 protein is a membrane glyco-protein expressed only in macrophages, and functions as divalent transition metal (iron and manganese) transporter. The activity of *SLC11A1* is directly linked with acidification of the phagolysosome, antigen recognition and activation of MHC, activation of cytokines, IL and TNF, and formation of granuloma.

Specific polymorphisms of *Slc11α1* have been associated with activation of macrophages and TNFa, resulting in heavier histopathological lesions compared to the wild-type gene, as well as hypersensitivity reactions resembling toxic-shock syndrome. The latter has been recorded in connection with leishmaniosis, toxoplasmosis and rheumatoid arthritis (El-Safi et al., 2006), (Castellucci et al., 2010), (de Vasconcelos et al., 2017).

The *Slc11α1*gene is located in chromosome CFA37 in the dog; its size is 9 Kb and includes a 700 base pair (bp) promoter region (Altet et al., 2002). A polymorphism in the

specific promoter region (145bp) has been associated with sensitivity to visceral leishmaniosis, though not conclusively (Altet et al., 2002), (Sanchez-Robert et al., 2005).

B) The genes coding the major histocompatability complex (*MHC*).

The specific group of genes is located in the mouse and human chromosome 17 and 6, respectively. In mouse, the *MHC* seems to determine the outcome of infection induced by all pathogenic *Leishmania* spp., and especially *Leishmania donovani* (Leclerq et al., 1996), (Quinnell et al., 2003), (Lemos et al., 2004), (Nylen et al., 2004). In the dog, the genotype *DLA-DRB1*, which is associated with *MHC*, and more specifically the allele DLA-DRB1*01502, has been linked with the development of heavy clinical disease, due to the production of high levels of leishmania-specific antibody (IgG), (Quinnell et al., 2003). The association between *MHC* and clinical severity of leishmaniosis is documented in humans in connection with the region corresponding to *MHCII*, and more specifically the coding region of the human leukocyte antigen [(HLA)-DRB1-HLA-DQA1], (Fakiola et al., 2013).

C) The gene coding the Nucleotide-binding oligomerization domain containing protein 2 (*NOD2*).

NOD2 belongs to the large *NLRs* family (*NOD-like receptors*) of the pattern recognition receptors (PRR), and induces activation of immune-regulatory genes, and production of factors capable of detaining the infection induced by leishmania, such as NF-κB, MAPK or inflammatory cytokines (Kawai and Akira, 2009). The *NOD2-RIP2* pathway is activated in humans and mice with visceral leishmaniosis, and evokes a *Th1* immune response (Nascimento et al., 2016). The exact opposite has been documented in connection with down-regulation of *NOD2*, which is linked with intracellular survival of *Leishmania infantum* (Turchetti et al., 2015).

D) The gene coding the streptococcal collagen-like protein (*Scl1*).

The *Scl1* is located in the mouse and human chromosome 11 and 17, respectively. In mouse, the *Scl1* has been associated with rapid healing of subcutaneous lesions, following infection by *Leishmania mexicana*. The genomic region that corresponds to *Scl1* also hosts certain other genes with immune-regulatory function, such as *Nos2*, which controls the release of cytokines from activated macrophages, and *JE*, *MIP1α*, *MIP1b* and *RANTES*, the activity of which is associated with chemotaxis (Roberts et al., 1990), (Mock et al., 1993), (Roberts et al., 1993), (Blackwell, 1996), (Loeuillet et al., 2016).

E) The gene coding the canine β-defensin-1 protein (*CBD1*).

Defensins are peptides with antimicrobial activity expressed in epithelial cells and lymphocytes (Hazlett and Wu, 2011). The specific proteins are probably the main chemotactic factor of dendritic cells; hence formulating adaptive immunity. Polymorphisms in *CBD1* have been associated in dog with specific pathologic conditions of the skin and lungs (Van Damme et al., 2009), (Erles and Brownlie, 2010), and more recently, with sensitivity to *Leishmania infantum* (da Silva et al., 2017). Considering however that the activity of dendritic cells is not strictly associated with resistance or sensitivity to intracellular infections, the role of *CBD1* needs to be elucidated (da Silva et al., 2017).

F) The gene coding the streptococcal collagen-like protein 2 (*Scl2*).

The *Scl2* is located in the mouse and human chromosome 4 and 9, respectively. Little is known about the activity of the specific gene, which has been linked in mouse with resistance to *Leishmania Mexicana* (Roberts et al., 1990). Based mainly on the location of *Scl2*, it is speculated that its activity is focused at the activation of JAKs (Janus tyrosine kinases) that induce macrophage activation through IFN-γ (Ihle and Kerr, 1995), (Blackwell, 1996), (Loeuillet et al., 2016).

Conclusions

The study of the genetic predisposition of humans and animals to leishmaniosis is necessary in clarifying disease pathogenesis. At the same time, the specific approach can improve the interpretation of serology testing with regards to disease prognosis and treatment response, and can thus have a strong positive impact on animal and public health protection.

References

Abranches, P., Silva-Pereira, M. C. D., Conceicao-Silva, F. M., Santos-Gomes, G. M., & Janz, J. G. (1991). Canine Leishmaniasis: Pathological and Ecological Factors Influencing Transmission of Infection. *The Journal of Parasitology*, *77*(4), 557. https://doi.org/10.2307/3283159

Altet, L. (2002). Mapping and Sequencing of the Canine NRAMP1 Gene and Identification of Mutations in Leishmaniasis-Susceptible Dogs. *Infection and Immunity*, *70*(6), 2763–2771. https://doi.org/10.1128/IAI.70.6.2763-2771.2002

Ansari, N. A., Ramesh, V., & Salotra, P. (2006). Interferon (IFN)–γ, Tumor Necrosis Factor–α, Interleukin-6, and IFN-γ Receptor 1 Are the Major Immunological Determinants Associated with Post–Kala Azar Dermal Leishmaniasis. *The Journal of Infectious Diseases*, *194*(7), 958–965. https://doi.org/10.1086/506624

Baneth, G., Koutinas, A. F., Solano-Gallego, L., Bourdeau, P., & Ferrer, L. (2008). Canine leishmaniosis – new concepts and insights on an expanding zoonosis: part one. *Trends in Parasitology*, *24*(7), 324–330. https://doi.org/10.1016/j.pt.2008.04.001

Barbieri, C. L. (2006). Immunology of canine leishmaniasis. *Parasite Immunology*, *28*(7), 329–337. https://doi.org/10.1111/j.1365-3024.2006.00840.x

Blackwell, J. M. (1996). Genetic susceptibility to leishmanial infections: studies in mice and man. *Parasitology*, *112*(S1), S67–S74. https://doi.org/10.1017/S0031182000076678

Blackwell, J. M., Searle, S., Mohamed, H., & White, J. K. (2003). Divalent cation transport and susceptibility to infectious and autoimmune disease: continuation of the Ity/Lsh/Bcg/Nramp1/Slc11a1 gene story. *Immunology Letters*, *85*(2), 197–203. https://doi.org/10.1016/S0165-2478(02)00231-6

Bourdoiseau, G., Bonnefont, C., Hoareau, E., Boehringer, C., Stolle, T., & Chabanne, L. (1997). Specific IgG1 and IgG2 antibody and lymphocyte subset levels in naturally Leishmania infantum-infected treated and untreated dogs. *Veterinary Immunology and Immunopathology*, *59*(1–2), 21–30. https://doi.org/10.1016/S0165-2427(97)00072-X

Castellucci, L., Jamieson, S.E., Miller, E.N., Menezes, E., Oliveira, J., Magalhães, A., Guimarães, L.H., Lessa, M., de Jesus, A.R., Carvalho, E.M., & Blackwell, J.M. (2010). Castellucci, L., Jamieson, S. E., Miller, E. N., Menezes, E., Oliveira, J., Magalhães, A., … Blackwell, J. M. (2010). CXCR1 and SLC11A1polymorphisms affect susceptibility to cutaneous leishmaniasis in Brazil: a case-control and family-based study. *BMC Medical Genetics*, *11*(1), 10. https://doi.org/10.1186/1471-2350-11-10

Cecilio, P., Pérez-Cabezas, B., Santarém, N., Maciel, J., Rodrigues, V., & Cordeiro da Silva, A. (2014). Deception and Manipulation: The Arms of Leishmania, a Successful Parasite. *Frontiers in Immunology*, *5*. https://doi.org/10.3389/fimmu.2014.00480

Chakour, R., Guler, R., Bugnon, M., Allenbach, C., Garcia, I., Mauel, J., … Tacchini-Cottier, F. (2003). Both the Fas Ligand and Inducible Nitric Oxide Synthase Are Needed for Control of Parasite Replication within Lesions in Mice Infected with Leishmania major whereas the Contribution of Tumor Necrosis Factor Is Minimal. *Infection and Immunity*, *71*(9), 5287–5295. https://doi.org/10.1128/IAI.71.9.5287-5295.2003

da Silva, L. G., Costa-Júnior, C. R. L., Figueiredo-Júnior, C. A. S., Leal-Balbino, T. C., Crovella, S., Otranto, D., … Dantas-Torres, F. (2017). Canine β-defensin-1 (CBD1) gene as a possible marker for Leishmania infantum infection in dogs. *Parasites & Vectors*, *10*(1), 199. https://doi.org/10.1186/s13071-017-2130-8

de Lima, V. M. F., Peiro, J. R., & de Oliveira Vasconcelos, R. (2007). IL-6 and TNF-α production during active canine visceral leishmaniasis. *Veterinary Immunology and Immunopathology*, *115*(1–2), 189–193. https://doi.org/10.1016/j.vetimm.2006.10.003

de Vasconcelos, T. C. B., Furtado, M. C., Belo, V. S., Morgado, F. N., & Figueiredo, F. B. (2019). Canine susceptibility to visceral leishmaniasis: A systematic review upon genetic aspects, considering breed factors and immunological concepts. *Infection, Genetics and Evolution*, *74*, 103293. https://doi.org/10.1016/j.meegid.2017.10.005

Desjeux, P., & Alvar, J. (2003). Leishmania /HIV co-infections: epidemiology in Europe. *Annals of Tropical Medicine & Parasitology*, *97*(1), 3–15. https://doi.org/10.1179/000349803225002499

Diaz, N. L., Fernandez, M., Figueira, E., Ramirez, R., Monsalve, I. B., & Tapia, F. J. (2003). Nitric oxide and cellular immunity in experimental cutaneous leishmaniasis. *Clinical and Experimental Dermatology*, *28*(3), 288–293. https://doi.org/10.1046/j.1365-2230.2003.01206.x

El-Safi, S., Kheir, M. M., Bucheton, B., Argiro, L., Abel, L., Dereure, J., … Dessein, A. (2006). Genes and environment in susceptibility to visceral leishmaniasis. *Comptes Rendus Biologies*, *329*(11), 863–870. https://doi.org/10.1016/j.crvi.2006.07.007

Erles, K., & Brownlie, J. (2010). Expression of β-defensins in the canine respiratory tract and antimicrobial activity against Bordetella bronchiseptica. *Veterinary Immunology and Immunopathology*, *135*(1–2), 12–19. https://doi.org/10.1016/j.vetimm.2009.10.025

Fakiola, M., Strange, A., Cordell, H. J., Miller, E. N., Pirinen, M., Su, Z., … Donnelly, P. (2013). Common variants in the HLA-DRB1–HLA-DQA1 HLA class II region are associated with susceptibility to visceral leishmaniasis. *Nature Genetics*, *45*(2), 208–213. https://doi.org/10.1038/ng.2518

Fondevila, D., Vilafranca, M., & Ferrer, L. (1997). Epidermal immunocompetence in canine leishmaniasis. *Veterinary Immunology and Immunopathology*, *56*(3–4), 319–327. https://doi.org/10.1016/S0165-2427(96)05755-8

França-Silva, J. C., da Costa, R. T., Siqueira, A. M., Machado-Coelho, G. L. L., da Costa, C. A., Mayrink, W., … Nascimento, E. (2003). Epidemiology of canine visceral leishmaniosis in the endemic area of Montes Claros Municipality, Minas Gerais State, Brazil. *Veterinary Parasitology*, *111*(2–3), 161–173. https://doi.org/10.1016/S0304-4017(02)00351-5

Goris, A., & Liston, A. (2012). The Immunogenetic Architecture of Autoimmune Disease. *Cold Spring Harbor Perspectives in Biology*, *4*(3), a007260–a007260. https://doi.org/10.1101/cshperspect.a007260

Gradoni, L. (2015). Canine Leishmania vaccines: Still a long way to go. *Veterinary Parasitology*, *208*(1–2), 94–100. https://doi.org/10.1016/j.vetpar.2015.01.003

Gramiccia, M., & Gradoni, L. (2005). The current status of zoonotic leishmaniases and approaches to disease control. *International Journal for Parasitology*, *35*(11–12), 1169–1180. https://doi.org/10.1016/j.ijpara.2005.07.001

Green, S. J., Crawford, R. M., Hockmeyer, J. T., Meltzer, M. S., & Nacy, C. A. (1990). Leishmania major amastigotes initiate the L-arginine-dependent killing mechanism in IFN-gamma-stimulated macrophages by induction of tumor necrosis factor-alpha. *Journal of Immunology*, *145*, 4290–4297.

Gregersen, P. K., & Olsson, L. M. (2009). Recent Advances in the Genetics of Autoimmune Disease. *Annual Review of Immunology*, *27*(1), 363–391. https://doi.org/10.1146/annurev.immunol.021908.132653

Gumy, A., Aseffa, A., Rachinel, N., Breton, M., Otten, L., Tacchini-Cottier, F., … Louis, J. (2006). LACK-reactive CD4+ T cells require autocrine IL-2 to mediate susceptibility toLeishmania major. *European Journal of Immunology*, *36*(6), 1465–1473. https://doi.org/10.1002/eji.200535801

Hazlett, L., & Wu, M. (2011). Defensins in innate immunity. *Cell and Tissue Research*, *343*(1), 175–188. https://doi.org/10.1007/s00441-010-1022-4

Ihle, J. N., & Kerr, I. M. (1995). Jaks and Stats in signaling by the cytokine receptor superfamily. *Trends in Genetics*, *11*(2), 69–74. https://doi.org/10.1016/S0168-9525(00)89000-9

Kawai, T., & Akira, S. (2009). The roles of TLRs, RLRs and NLRs in pathogen recognition. *International Immunology*, *21*(4), 317–337. https://doi.org/10.1093/intimm/dxp017

Kochi, Y. (2016). Genetics of autoimmune diseases: perspectives from genome-wide association studies: Table 1. *International Immunology*, *28*(4), 155–161. https://doi.org/10.1093/intimm/dxw002

Leclercq, V., Lebastard, M., Belkaid, Y., Louis, J., & Milon, G. (1996). The outcome of the parasitic process initiated by Leishmania infantum in laboratory mice: a tissue-dependent pattern controlled by the Lsh and MHC loci. *Journal of Immunology*, *157*, 4537–4745.

Lemos, M. P., Esquivel, F., Scott, P., & Laufer, T. M. (2004). MHC Class II Expression Restricted to CD8α+ and CD11b+ Dendritic Cells Is Sufficient for Control of Leishmania major. *The Journal of Experimental Medicine*, *199*(5), 725–730. https://doi.org/10.1084/jem.20030795

Loeuillet, C., Bañuls, A.-L., & Hide, M. (2016). Study of Leishmania pathogenesis in mice: experimental considerations. *Parasites & Vectors*, *9*(1), 144. https://doi.org/10.1186/s13071-016-1413-9

Mock, B., Blackwell, J., Hilgers, J., Potter, M., & Nacy, C. (1993). Genetic control of *Leishmania major* infection in congenic, recombinant inbred and F2 populations of mice. *European Journal of Immunogenetics*, *20*(5), 335–348. https://doi.org/10.1111/j.1744-313X.1993.tb00153.x

Nascimento, M. S. L., Ferreira, M. D., Quirino, G. F. S., Maruyama, S. R., Krishnaswamy, J. K., Liu, D., … Silva, J. S. (2016). NOD2-RIP2–Mediated Signaling Helps Shape Adaptive Immunity in Visceral Leishmaniasis. *Journal of Infectious Diseases*, *214*(11), 1647–1657. https://doi.org/10.1093/infdis/jiw446

Nylén, S., & Gautam, S. (2010). Immunological perspectives of leishmaniasis. *Journal of Global Infectious Diseases*, *2*(2), 135. https://doi.org/10.4103/0974-777X.62876

Nylen, S., Maasho, K., McMahon-Pratt, D., & Akuffo, H. (2004). Leishmanial Amastigote Antigen P-2 Induces Major Histocompatibility Complex Class II-Dependent Natural Killer-Cell Reactivity in Cells from Healthy Donors. *Scandinavian Journal of Immunology*, *59*(3), 294–304. https://doi.org/10.1111/j.0300-9475.2004.01388.x

Paccagnini, D., Sieswerda, L., Rosu, V., Masala, S., Pacifico, A., Gazouli, M., … Sechi, L. A. (2009). Linking Chronic Infection and Autoimmune Diseases: Mycobacterium avium Subspecies paratuberculosis, SLC11A1 Polymorphisms and Type-1 Diabetes Mellitus. *PLoS ONE*, *4*(9), e7109. https://doi.org/10.1371/journal.pone.0007109

Pinelli, E., Killick-Kendrick, R., Wagenaar, J., Bernadina, W., Del Real, G., & Ruitenberg, J. (1994). Cellular and humoral immune responses in dogs experimentally and naturally infected with Leishmania infantum. *Infection and Immunity*, *64*, 229–235.

Pradhan, V., Borse, V., & Ghosh, K. (2010). PTPN22 gene polymorphisms in autoimmune diseases with special reference to systemic lupus erythematosus disease susceptibility. *Journal of Postgraduate Medicine*, *56*(3), 239. https://doi.org/10.4103/0022-3859.68651

Quinnell, R. J., Kennedy, L. J., Barnes, A., Courtenay, O., Dye, C., Garcez, L. M., … Ollier, W. E. R. (2003). Susceptibility to visceral leishmaniasis in the domestic dog is associated with MHC class II polymorphism. *Immunogenetics*, *55*(1), 23–28. https://doi.org/10.1007/s00251-003-0545-1

Roberts, M., Alexander, J., & Blackwell, J. M. (1990). Genetic analysis of *Leishmania mexicana* infection in mice: single gene (Scl-2) controlled predisposition to cutaneous lesion development. *European Journal of Immunogenetics*, *17*(1–2), 89–100. https://doi.org/10.1111/j.1744-313X.1990.tb00862.x

Roberts, M., Mock, B. A., & Blackwell, J. M. (1993). Mapping of genes controlling *Leishmania major* infection in CXS recombinant inbred mice. *European Journal of Immunogenetics*, *20*(5), 349–362. https://doi.org/10.1111/j.1744-313X.1993.tb00154.x

Sanchez-Robert, E. (2005). Polymorphism of Slc11a1 (Nramp1) Gene and Canine Leishmaniasis in a Case-Control Study. *Journal of Heredity*, *96*(7), 755–758. https://doi.org/10.1093/jhered/esi111

Sanjeevi, C. B., Miller, E. N., Dabadghao, P., Rumba, I., Shtauvere, A., Denisova, A., … Blackwell, J. M. (2000). Polymorphism at NRAMP1 and D2S1471 loci associated with juvenile rheumatoid arthritis. *Arthritis & Rheumatism*, *43*(6), 1397–1404. https://doi.org/10.1002/1529-0131(200006)43:6<1397::AID-ANR25>3.0.CO;2-6

Searle, S., & Blackwell, J. M. (1999). Evidence for a functional repeat polymorphism in the promoter of the human NRAMP1 gene that correlates with autoimmune versus infectious disease susceptibility. *Journal of Medical Genetics*, *36*, 295–299.

Srivastava, S., Pandey, S. P., Jha, M. K., Chandel, H. S., & Saha, B. (2013). Leishmania expressed lipophosphoglycan interacts with Toll-like receptor (TLR)-2 to decrease TLR-9 expression and reduce anti-leishmanial responses. *Clinical & Experimental Immunology*, *172*(3), 403–409. https://doi.org/10.1111/cei.12074

Stager, S., Alexander, J., Carter, K. C., Brombacher, F., & Kaye, P. M. (2003). Both Interleukin-4 (IL-4) and IL-4 Receptor Signaling Contribute to the Development of Hepatic Granulomas with Optimal Antileishmanial Activity. *Infection and Immunity*, *71*(8), 4804–4807. https://doi.org/10.1128/IAI.71.8.4804-4807.2003

Theodoropoulos, G., & Theis, J. H. (1989). Decrease of acid phosphatase activity in murine peritoneal macrophages infected with Leishmania donovani. *International Journal for Parasitology*, *19*(7), 813–816. https://doi.org/10.1016/0020-7519(89)90071-4

Tripathi, P., Ray, S., Sunder, S., Dube, A., & Naik, S. (2006). Identification of Leishmania donovani antigens stimulating cellular immune responses in exposed immune individuals. *Clinical and Experimental Immunology*, *143*(2), 380–388. https://doi.org/10.1111/j.1365-2249.2005.03000.x

Turchetti, A. P., da Costa, L. F., Romão, E. de L., Fujiwara, R. T., da Paixão, T. A., & Santos, R. L. (2015). Transcription of innate immunity genes and cytokine secretion by canine macrophages resistant or susceptible to intracellular survival of Leishmania infantum. *Veterinary Immunology and Immunopathology*, *163*(1–2), 67–76. https://doi.org/10.1016/j.vetimm.2014.11.010

Turchetti, A. P., da Costa, L. F., Romão, E. de L., Fujiwara, R. T., da Paixão, T. A., & Santos, R. L. (2015). Transcription of innate immunity genes and cytokine secretion by canine macrophages resistant or susceptible to intracellular survival of Leishmania infantum. *Veterinary Immunology and Immunopathology*, *163*(1–2), 67–76. https://doi.org/10.1016/j.vetimm.2014.11.010

van Damme, C. M. M., Willemse, T., van Dijk, A., Haagsman, H. P., & Veldhuizen, E. J. A. (2009). Altered cutaneous expression of β-defensins in dogs with atopic dermatitis. *Molecular Immunology*, *46*(13), 2449–2455. https://doi.org/10.1016/j.molimm.2009.05.028

Vidal, S. M., Malo, D., Vogan, K., Skamene, E., & Gros, P. (1993). Natural resistance to infection with intracellular parasites: Isolation of a candidate for Bcg. *Cell*, *73*(3), 469–485. https://doi.org/10.1016/0092-8674(93)90135-D

WHO, (2010). In Technical Report Series 949. Control of Leishmaniases: report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22–26 March 2010

WHO, (2018). World Health Organisation https://www.who.int/news-room/fact-sheets/detail/leishmaniasis.

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