Laboratory of Molecular and Cellular Immunology

Genetics of pathogenesis of leishmaniasis, gene mapping, functional diversity, general and species-specific control

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The research programme of the laboratory aims to identify genes and molecular mechanisms involved in the control of immune response and susceptibility to complex infectious diseases. We focus on complex diseases because they are responsible for the largest part of human morbidity and mortality. They are controlled by multiple genes and hence their pathogenesis cannot be explained by effects of a single gene with omission of others. *Leishmaniasis* is such a complex disease and it has served as a major paradigm of immune response to an infectious agent. We aim to identify the genes and functions controlling this disease. The disease is caused by protozoan parasites of genus *Leishmania* that multiply in macrophages. Different species of *Leishmania* induce different symptoms, but even the patients infected by the same species develop different clinical manifestations. Many phenomena observed in human leishmaniases can be investigated in the mouse. Our approach uses a combination of genetic dissection with screening of a large set of immunological and clinical parameters of the disease. The majority of our data have been obtained using infection of *L. major*. Recently, we established the first genetic model of susceptibility to *L. tropica* and provided the first insight into the genetic architecture of susceptibility to this parasite. We have described eight loci on seven chromosomes and shown that the presence of individual symptoms of the disease is controlled by different subsets of the host's genes. The identification of the host's genes responsible for the specific symptoms of the disease induced by different *Leishmania* species will contribute to the understanding of the mechanisms of pathogenesis of leishmaniasis, similarly as comparative parasite genomics led to the identification of differentially distributed genes in *Leishmania* species inducing different pathology, and analysis of specific virulence factors revealed how different *Leishmania* species subvert or circumvent the host's defences. Such analysis will provide description of individual predisposition to specific symptoms of the disease and its probable course. Moreover, the possibility to compare genetics of the response to several *Leishmania* species will further help to understand the genetic basis of general and species-specific responses of the host. This will synergize with the future information on the genome sequence of *L. tropica* and interaction of its specific virulence factors with the immune system. Last but not the least: we have established a novel model for studying tick-borne encephalitis, the main tick-borne virus infection in Eurasia.

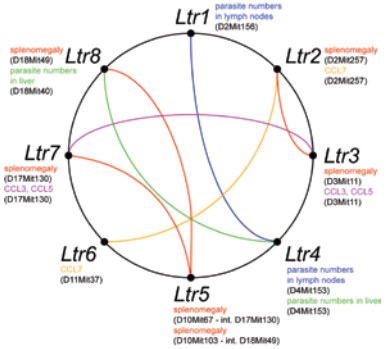


Fig. 1. Epistasis in control of susceptibility to *Leishmania tropica*
Phenotypes controlled by each locus are shown at their symbol in different colours. The coloured lines connecting the loci indicate interactions controlling the specific phenotypes.

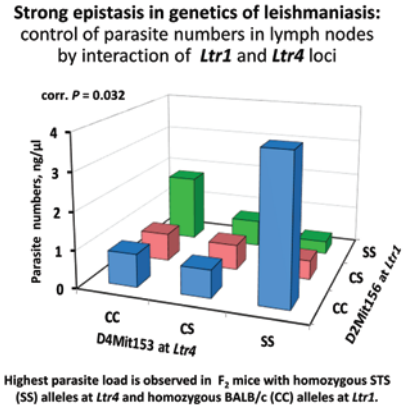
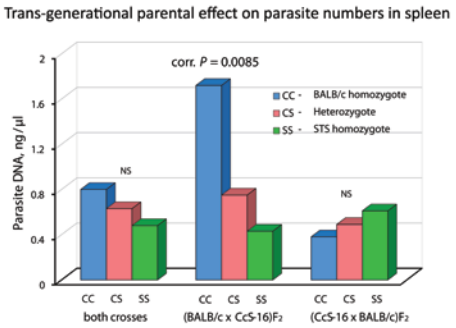


Fig. 2. Interacting loci *Ltr1* and *Ltr4*

Highest parasite load is observed in F_2 mice with homozygous STS (SS) alleles at *Ltr4* and homozygous BALB/c (CC) alleles at *Ltr1*.



Locus *Ltr3* linked to D3Mit25 influencing parasite numbers in spleen was significant only in the cross (BALB/c x CcS-16)F_2, but not in the cross (CcS-16 x BALB/c)F_2.

- GACR, GAP502/11/2116 – Differences in the clinical course of tick-borne encephalitis in the host and their genetic determination, 2011-2015, M. Lipoldová
- MEYS, LH12049 LH-KONTAKT – New genomic strategy for rapid identification of genes controlling development of infections and cancer, 2012-2015, M. Lipoldová
- GACR, GP13-41002P – Genetic control of parasite dissemination after *Leishmania* major infection, 2013-2015, T. Kobets
- GACR, 14-35944P – Analysis of interaction between *Leishmania* major and macrophages of susceptible and resistant mouse strains, 2014-2015, I. Grekov
- GACR, 14-30186S – Hidden relevant functional pathways in host response to *Leishmania* infection revealed in focused genomic constructions, 2014-2016, M. Lipoldová

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2. Lipoldová M: Giardia and Vilém Dušan Lambl. **PLoS Negl Trop Dis 2014**.
3. Palus M, Vojtíšková J, Salát J, Kopecký J, Grubhoffer L, Lipoldová M, Demant P, Růžek D: Mice with different susceptibility to tick-borne encephalitis virus infection show selective neutralizing antibody response and inflammatory reaction in the central nervous system. **J Neuroinflammation 2013** 10(1): 77.
4. Sohrabi Y, Havelková H, Kobets T, Šíma M, Volkova V, Grekov I, Jarošíková T, Kurey I, Vojtíšková J, Svobodová M, Demant P, Lipoldová M: Mapping the genes for susceptibility and response to *Leishmania tropica* in mouse. **PLoS Negl Trop Dis 2013** 7(7): e2282.

First row from the left: Tetyana Kobets, PhD / Postdoctoral Fellow, Tereza Pokorná, Bc/ Diploma Student (since September 2014), Marie Lipoldová, Assoc Prof, PhD / Head of Laboratory, V. Volkova
Second row from the left: Lucie Kocandová, MSc / PhD Student (since October 2014), Yahya Sohrabi, PhD / Postdoctoral Fellow, Matyáš Šíma, MSc / PhD Student

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