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. We detected 21 *Lmr* (*Leishmania major* response) genes and mapped them to distinct chromosomal loci and we found that gene effects on the disease symptoms were organ-specific and heterogeneous. These 21 individual *Lmr* loci control 17 different combinations of pathological and immunological symptoms. Eight loci control both organ pathology and immunological parameters and 13 only immune reactions. Fifteen *Lmr* loci are involved in one or more genetic interactions, showing that gene interactions are common in response to *L. major*. Moreover, parasite elimination, immunological response, and pathological symptoms are regulated independently. Thus, these studies revealed a network-like complexity of the combined effects of the multiple functionally diverse QTLs (quantitative trait loci). Recently, we established the first genetic model of susceptibility to *L. tropica*, a species that similarly as *L. major* causes cutaneous leishmaniasis in humans, but can also visceralize and cause systemic illness. Comparison of the response to *L. major* and *L. tropica* in mouse strains revealed clearly different patterns in the strains' susceptibility to *L. tropica* and *L. major*, which demonstrates existence of species-specific controlling host genes with different functions. This information provides the first step to distinguishing the species-specific from the general genes controlling pathogenesis of leishmaniasis. Therefore, without combining the two components of variation involved in the outcome of *Leishmania* infection – genetic variation of the host and species of the parasite – the understanding of the mechanisms of disease will remain incomplete.

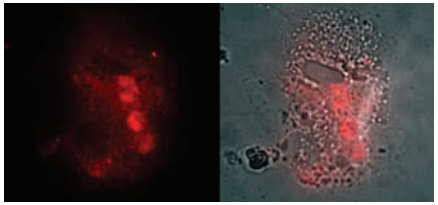

Fig. 1. ROX (Reactive Oxygen) expression in the macrophage after LPS stimulation and *L. major* infection detected with CellROX® Deep Reagent.

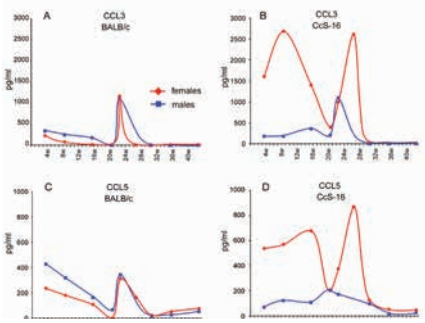

Fig. 2. Unique systemic chemokine response of females of strain CcS-16 after infection with *Leishmania tropica*.

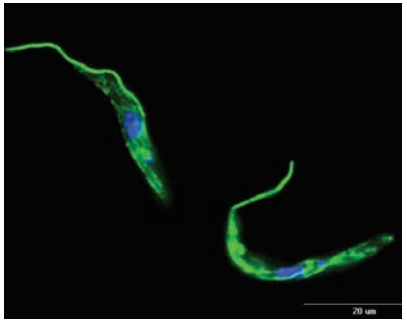

Fig. 3. *Trypanosoma brucei brucei*.

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- GA CR, GA310/08/1697 - First genetic model for analysis of susceptibility to parasite *Leishmania tropica*: potential implications for studies of human leishmaniases, 2008-2012, M. Lipoldová
- GA CR, GAP502/11/2116 - Differences in clinical course of tick-borne encephalitis in host, and their genetic determination, 2011-2015, M. Lipoldová
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