Laboratory of Molecular and Cellular Immunology

Functional gene mapping, leishmaniasis, atopy

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The research programme of the laboratory aims to identify genes and molecular mechanisms involved in 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 and their genetic analysis is subject of an intensive international effort. 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 *Leishmania major* infection in mouse. Our approach uses a combination of genetic dissection with screening of a large set of immunological and clinical parameters of the disease. We mapped 21 *Lmr* (*Leishmania major* response) loci and found that gene effects on 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 and pathological processes are regulated independently. In conclusion, these studies revealed a network-like complexity of the combined effects of the multiple functionally diverse QTLs (quantitative trait loci).

Lmr loci are likely relevant also for other diseases. Interestingly, nine of ten *Lmr* that influence serum IgE level after *Leishmania major* infection were mapped in the regions homologous with the human chromosomal segments that control total serum IgE in human atopic diseases. However, for the Lmr9 locus, the homologous human regions have not been connected with atopy. Thus, this locus may point to hitherto undetected human genes that are relevant for atopy. Indeed, in the position homologous to *Lmr9* on chromosome 8q12 we demonstrated a novel human IgE-controlling locus. This finding shows precision and predictive power of mouse models in investigation of complex traits in humans.

Fig. 1. Cutaneous leishmaniasis.

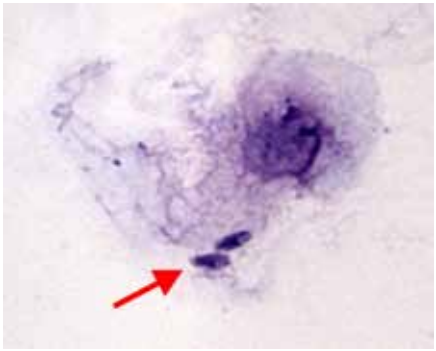

Fig. 2. *Leishmania* parasites in macrophage.

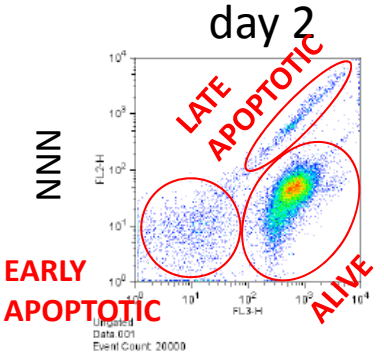

Fig. 3. *Leishmania* stained with propidium iodide and LDS 751.

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