6. Summary

Influence of the genetic background on the jejunal pathology following oral infection with *Yersinia enterocolitica* in mice

Extensive basic knowledge on inbred mouse strains and specific mouse mutants is essential to use mouse models in biomedical science. The specific genetic background of the different inbred mouse strains is known to be responsible for the considerable variations in the reaction of mice to infections, such as *Yersinia* infections. This observation indicated that differences in intensity and characteristics of the immune response between mouse strains should also exist on histological level.

On the one hand, this study aimed at adding to the data on basic knowledge of inbred mouse strains. On the other hand, histological evidence was to be provided of qualitative and quantitative differences in the examined inbred mouse strains' reaction to an infection with *Y. enterocolitica*. Subsequently, an order of susceptibility and, for the first time, also of the immunity of the studied mouse strains was established.

In the present study, four inbred wild-type mouse strains (C57BL/6OlaHsd, BALB/cOlaHsd, C3H/HeNHsd and $129P_2$/OlaHsd) were orally infected with a low-virulence strain of *Y. enterocolitica*. A systematic histopathomorphological analysis of the aboral small intestine was performed three and nine days p.i. The main focus was the characterization of the type and degree of inflammatory reactive patterns and the number and distribution of Yersinia colonies. Specifically, the influences of genetic backgrounds, gender and time point after infection were assessed.

Yersinia colonies and the changes in the tissue associated with the *Yersinia* infection were detected in all mouse strains in the mucosa as well as in the PP. Qualitative and quantitative differences in the inflammatory response, the colonies' distribution and the course of colony number were recorded between the different inbred mouse strains. For the first time, this study could demonstrate histopathologically that the inbred mouse strains studied differed in the character of the inflammatory changes.

In the present study, C57BL/6OlaHsd was classified as intermediate susceptible because of its high number of colonies and as strain with the best immunity. The bacteria were eliminated by a strong, effective immune response during infection. Macrophages could be detected very early. Furthermore, a partial recovery by granulation tissue and perivascular plasma cell infiltrates was observed histologically.

The strain BALB/cOlaHsd showed high resistance to the initial infection and the least effective immunity of the present study. Three days p.i., there were relatively low colony numbers but the strain did not show any maturation of the inflammatory response. The number of bacterial colonies and altered PP even increased during the infection. Similar purulent changes of the tissue were observed at both time points of examination. Organisation of the alterations hardly occured, and the plasma cell infiltration into the PP did not increase significantly. The animals of this strain were thus not able to confine the infection.

The strain C3H/HeNHsd was classified as the most susceptible strain with an intermediate, delayed immunity. At the beginning, the strong immune response was rather destructive. Three days p.i. macrophages and granulation tissue were hardly observed. The bacteria infected the mucosa and the PP to a similar extent. Despite an early organisation of the defects, an infiltration of the PP with plasma cells and a reduction of the bacterial colonies, the number of colonies was still relatively high nine days p.i.

The strain $129P_2$/OlaHsd was classified as rather resistant because of the low number of colonies three days p.i. All in all, only relatively few PP were affected and colonized by *Yersinia*. The success of the individuals' immune responses varied to a great extent, and the immunity of this strain was classified as intermediate. The histological appearance of some of the animals was comparable to the C57BL/6OlaHsd animals, others were similar to BALB/cOlaHsd.

In the present study, several factors were discussed as possible causes for resistance and immunity of inbred mouse strains. Developing a T_H1 immune response at different intensities and the corresponding delayed formation of T_H1 cytokines might explain the different histopathologically detectable reactions in this study, too. In this context, IFN-γ and TNF-α levels and the mediation of their biological activity are of outstanding importance for the efficicacy of the inflammatory response. A differing number of macrophages which are essential for the confinement of *Yersinia* infection, or their delayed activation or reduced functionality might lead to a decreased reduction of bacteria and consequently to a persistence or even an exacerbation of the infection. An early activation of the T-lymphocytes to trigger the T_H1 immune response may play a decisive role and is exhibited at varying degrees in the inbred mouse strains. Different proliferation of CD4+ and CD8+ T cells and their homing in the PP as well as the different organisation ability of the altered tissue might be additional factors contributing to the differing immune responses of the investigated mouse strains. Differences in the expression or response of a multitude of chemokines, chemokine receptors and adhesion molecules in the mouse strains might lead to the different influxes of immune cells. It is, furthermore, conceivable that factors of bacterial virulence (e.g. LcrV, rovA, Yops, etc.) are differently effective in the different mouse strains in finding their receptors or target structures to modulate the immune response and to consequently establish survival in the host.

In the present study, basic data on inbred mouse strains in term of their reaction to an infection with *Y. enterocolitica* were established and qualitative as well as quantitative differences were detected on the histological level. Finally, a differentiated order of susceptibility and, for the first time, also of the immunity of the studied mouse strains was established based on histological evidence.