Systemic Vaccination with Aluminum Hydroxide Induces Protective Immunity against Helicobacter Pylori Infection in Mice

H. pylori infection causes gastritis, ulcers, MALT lymphoma and gastric cancer. Since the prevalence of infection is high (50 to 80% worldwide) and pharmacological eradication therapy has several disadvantages, much effort has been undertaken to develop a preventative vaccine. Because the mucosal immune system is thought to be a rather autonomous entity, research has been focussed on mucosal immunization. However, mucosal adjuvants (e.g. cholera toxin) are too toxic for use in humans.

I investigated whether protection against Helicobacter infection can be achieved by systemic immunizations with the adjuvants Aluminum Hydroxide (ALOH), which is licensed for human use and the experimental adjuvant CFA. Using the H. felis and H. pylori mouse models I first characterized the immune response to our vaccines by ELISPOT and ELISA assay: Immunization with Helicobacter antigen and AlOH induced IL-5 secreting, antigen-specific T cells and low levels of IgG2a, thus eliciting a type-2 immune response. The adjuvant CFA led to induction of IFN-γ secreting, antigen-specific T cells and high levels of IgG2a, which is characteristic for type-1 immune responses. Both immune responses conferred protection after challenge with live Helicobacter organisms, as confirmed by the complete absence of any bacteria in histological sections of the stomach and culture of gastric biopsy samples. Next I studied the mechanism of protection: Antibodies are not required for protective immunity since IgG109 MT (immunoglobulin-gene knockout) mice are protected against Helicobacter infection after immunization with antigen and AlOH. Protective immunity can be transferred to otherwise immunodeficient rag1-/- mice by CD4+ T cells from mice previously immunized with antigen and AlOH. However, adoptive transfer of CD4+ spleen T cells from mice immunized with antigen and CFA into rag1-/- mice did not elicit protection against infection.

In summary, I have demonstrated that systemic immunization with Alum as adjuvant induces protective immunity against H. pylori in mice which is mediated by CD4+ type-2 T cells. Perhaps the most important aspect of this work is that systemic immunization can result in mucosal immunity. This has a direct impact on the development of a vaccine against Helicobacter and other mucosal pathogens. The fact that protective immunity in our model is antibody (i.e. IgA)-independent and can be transferred by CD4+ T cells suggests the existence of a novel CD4+ T cell-mediated effector mechanism at the gastric mucosa. We found that type-1 and type-2 immunity are equally protective when wild type mice are immunized. In adoptive transfer studies, however, only type-2 immunity seemed to be protective, possibly due to the absence of certain regulatory networks in rag1-/- mice. Further advantages of the type-2 adjuvant Alum are its low cost and its safety for use in humans.
The notion put forth in this work, that systemic immunization with *Helicobacter* antigens in Alum is suited to induce immune protection that has been accomplished previously only by the use of toxic mucosal adjuvants, should expedite the development of a *H. pylori* vaccine.