

The Immunology of *Bordetella pertussis* Infection



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Despite the wealth of information on the pathogenesis, virulence and antigenicity of *Bordetella pertussis* and the successful development of efficacious acellular pertussis vaccines, the mechanism of vaccine induced protection against *Bordetella pertussis* in man is still poorly understood. Using murine models, we and others have previously reported evidence of the involvement of T cells in protective immunity. Based on the observation that respiratory infection with *Bordetella pertussis* induces potent and persistent immunity, we have studied the induction of T cell subsets induced by natural infection or by immunization with whole cell and acellular vaccines in children. Furthermore we have employed the murine respiratory challenge model in experiments that permitted manipulation of the immune system in an attempt to provide more direct evidence for the role of distinct arms of the immune response in protection against *Bordetella pertussis*.

Through collaboration with Jann Storsaeter, Lennart Nillson and Lief Gothefors in Sweden, Knut Øymar in Norway, Elizabeth Miller in London and Fiona Shackley in Oxford, we have gained access to valuable clinical samples for the assessment of cellular immune responses to *Bordetella pertussis* in children. Initial investigations of cytokine production by peripheral blood T cells from children recovering from whooping cough suggested that immunity generated by natural infection is mediated by Th1 cells. Furthermore analysis of blood samples from children within 3 months or 4 years of immunization with whole cell pertussis vaccine revealed a similar cytokine profile, moderate to high levels of IFN- γ , but undetectable IL-5. In contrast, analysis of cellular responses from children immunized with acellular vaccines demonstrated that primed T cells secreted high levels of IFN- γ and IL-5 following specific antigen stimulation *in vitro*. All of the high efficacy acellular

vaccines tested (SmithKline Beecham 3-component, Chiron Biocine 3-component and Connaught 5-component) produced this Th0 or mixed Th1/Th2 cytokine profile in the majority of children tested.

Access to clinical lots of pertussis vaccines has allowed us to validate our murine respiratory challenge model; the rate of bacterial clearance following aerosol challenge correlated with estimates of efficacy from clinical trials. Furthermore, the immune responses induced in mice were consistent with our demonstration that acellular and whole cell vaccines induced distinct T cell populations in children. In mice, the acellular vaccine induced T cells that secreted IL-5 and IL-4 after *in vitro* culture, but undetectable IFN- γ and low levels of IL-2, a clear Th2 cytokine profile, whereas, the whole cell vaccine induced a clear Th1 response. Recent experiments using immunoglobulin, IL-4, or IFN- γ receptor gene knockout mice have suggested that Th1 responses are important for bacterial clearance following primary infection and in immunity induced with a whole cell vaccine, whereas antibody and Th2 cells play a more critical role in the protective mechanism of the acellular vaccines. Furthermore strategies that can shift the immune response induced with acellular vaccine from Th2 to Th1, such as the use of an S-1 recombinant PT mutant or the inclusion of IL-12 in the formulation, were found to enhance the rate of bacterial clearance following bacterial challenge. In conclusion, our current understanding of immunity to *Bordetella pertussis* suggests that anti-*Bordetella pertussis* IgG antibodies play a key role in preventing bacterial adherence and that *Bordetella pertussis*-specific T cells (probably IL-4 and IL-5 secreting Th0/Th2 cells) are required for the induction of this humoral response, whereas Th1 cells function in limiting the course of infection through enhanced bacterial uptake and killing by phagocytic cells.