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Samenvatting proefschrift "CD4+ T cel respons na kinkhoestinfectie en vaccinatie"

Abstract Thesis 'CD4+ T cel response after pertussis infection and vaccination'

Korte Nederlandse samenvatting

De toename van kinkhoestgevallen in de laatste decennia laten zien dat de duur van bescherming na vaccinatie niet levenslang is. Eén van de onderliggende redenen kan het opwekken van een suboptimale immuunrespons door de huidige vaccins zijn. De studies in dit promotieonderzoek hebben bijgedragen tot het verkrijgen van meer inzicht in de eigenschappen die de kinkhoestbacterie-specifieke immuunrespons moet hebben om langdurige en effectieve bescherming te bieden. De studies zijn vooral gefocust op een celtype van het adaptieve immuunsysteem dat een geheugenrespons kan vormen tegen de kinkhoestbacteriën, namelijk de CD4+ T cel.

Er zijn verschillende muismodellen en 'omics' onderzoekstechnieken ontwikkeld en geoptimaliseerd waarmee verschillen tussen effectieve en minder effectieve kinkhoestbacterie-specifieke immuunresponsen gedetailleerd in kaart kunnen worden gebracht. Kinkhoestinfectie wekt een type CD4+ T cel respons op die geassocieerd wordt met de meest langdurige bescherming, maar de respons na vaccinatie met de huidige kinkhoestvaccins wijkt hiervan af. Het toevoegen van een extra adjuvant aan de huidige vaccins kon de opgewekte CD4+ T cel respons wel sturen naar een respons vergelijkbaar met die na infectie. Een nog verdere verbetering werd bereikt met een nieuwe generatie vaccin, een zogenaamd outer-membrane vesicle vaccin, vooral wanneer dit vaccin direct in de longen van de muizen werd toegediend.

De fundamentele kennis die verkregen is in dit onderzoek kan bijdragen aan de ontwikkeling van nieuwe kinkhoestvaccins en vaccinatiestrategieën. Daarnaast is deze kennis belangrijk ter ondersteuning van de overheid voor haar beleid rondom de preventie van kinkhoest door middel van vaccinatie.

English abstract

The introduction of whole cell pertussis (wP) vaccines in the 1950s led to a massive decrease in pertussis incidence and mortality. However, since a few decades, resurgence of pertussis is observed in highly vaccinated populations. Several explanations have been proposed to underlie the resurgence of pertussis, including pathogen adaptation and waning vaccine-induced immunity, especially after vaccination with currently used acellular pertussis (aP) vaccines. Suboptimal protection by aP vaccines may be caused by the induction of (i) an immune response with a narrow-specificity since it only contains 1-5 antigens, (ii) a suboptimal functional programming of the CD4 T cell response, (iii) end-stage differentiation of the CD4 T cells most likely due to the high antigen

concentrations, (iv) and absence of mucosal immune responses in the respiratory tract. In this thesis, several alternative approaches for current pertussis vaccination were tested in mice and compared by using innovative and systems based technologies, with the main focus to understand the molecular basis for the different outcomes in the CD4+ T helper cell (Th) response. By applying these technologies, detailed molecular signatures of B. pertussis infection-induced immune responses, known to provide relatively durable protection, could be obtained in mice. This showed infection eventually led to the induction of a Th1 and Th17 CD4+ T cell response. In contrast, vaccination with the current aP vaccines led to the induction of a Th2-dominated response. This might be due to the fact that the aP vaccines do not contain Th1 and Th17 skewing pathogen-associated molecular patterns (PAMPs). Addition of a non-toxic lipopolysaccharide derivative, a PAMP that activates pattern-recognition receptor Toll-like receptor 4, to the aP vaccine induced, based on cytokine secretion, a shift from a Th2 towards a Th1 and Th17 response. Yet at the gene expression level, no difference in expression of Th2-associated genes, but only upregulation of Th1- and Th17-associated genes was observed. A new generation candidate vaccine, an outer-membrane vesicle (OMV) vaccine, circumvented the suboptimal functional programming of the CD4+ T cells and in addition also some other shortcomings of the aP vaccines. This OMV vaccine has a broad antigen composition and contains PAMPs. Pulmonary rather than subcutaneous administration of this vaccine led to a more effective protective immune response, based on molecular signatures and Th cell outcome, comparable to that after B. pertussis infection. In conclusion, improved pertussis vaccines, should include Th1 and Th17 skewing PAMPs or adjuvants and a broad antigen composition. Moreover, to provide long-term protective immunity against infection careful evaluation of the functional programming and memory potential of the induced specific CD4+ T cells is required. This thesis improved our insight into the immunological signatures and features of CD4+ T cell programming that are key for induction of protective immunity to B. pertussis and are relevant for the design of new types of pertussis vaccines. Yet there is a long road ahead in the development and implementation of such vaccines.

Keywords
Pertussis, Bordetella pertussis, Vaccination, CD4+ Tcells, Lipopolysaccharide, OMV, Mucosal immune response.

Main conclusions
It is important to evaluate the immunological signatures and CD4+ T cell programming capacity of new pertussis vaccines since only molecular pathways that lead to a mixed Th1 and Th17 response confer optimal protection. The Th2 dominance in the acellular pertussis vaccine-induced CD4+ T cell response can be dampened by addition of a TLR4 ligand, which skews the specific response towards a more effective Th1 and Th17 response. Novel outer-membrane vesicle pertussis vaccines have been shown to induce such a favorable Th1 and Th17 response and when administered in the respiratory tract can induce a mucosal immune response comparable with that induced by B. pertussis infection.

Main recommendations
Selection of new pertussis vaccines to be implemented into national immunization programs should be based on their immunological profile, their content of PAMPs or adjuvants, and a broad antigen composition with an optimized dosage.

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