Universität Basel

Research Project

Blockade of interferon-lambda signalling - a novel class of adjuvants to improve vaccine-induced antibody responses

Third-party funded project

Project title Blockade of interferon-lambda signalling - a novel class of adjuvants to improve vaccine-induced antibody responses
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Blockade of interferon-lambda signalling – a novel class of adjuvants to improve vaccine-induced antibody responses. Vaccination reduces the burden of many infectious diseases including infections with influenza viruses. Seroconversion may, however, be inadequate in specific populations as young children, pregnant women, the elderly, and patients with immunosuppression. Adjuvants act to boost the immune response. Nevertheless, most adjuvants induce nonspecific inflammation as opposed to a specific modulation of immune signalling. Novel adjuvants with an optimized and tailored activity profile are required. Antigen presenting cells are crucial for the interplay between innate and adaptive immunity and therefore ideal targets for adjuvants. Interferon (IFN)-alpha and -lambda activate and polarize macrophages and dendritic cells, which later regulate the priming of T- and B-cells. IFN-lambda is a newly discovered class of IFN and its effects in the context of vaccination have not been explored in detail. Single nucleotide polymorphisms (SNPs) in the IL-28B (IFN-lambda3) promoter region have a minor allele frequency of up to 40% in Caucasians and may alter vaccine-induced immunity - possibly impacting vaccination schedules. Own research: Interestingly, in solid organ transplant recipients with a SNP in the IL-28B promoter region (rs8099917, TG or GG) a significantly increased rate of seroconversion following influenza vaccination was observed. The rs8099917 TG and GG SNP is associated with a lower influenza-induced IL-28B gene expression. This suggests that a lower IL28B expression could lead to a reduced humoral immune response. Indeed, recombinant IL-28B reduced H1N1-induced Th2 cytokines, B-cell proliferation and antibody secretion. Next, we designed antagonistic peptides to block the IFN-lambda signaling. This increased the in vitro antibody secretion of PBMCs. Therefore, blockade of IFN-lambda may represent a novel adjuvant method to improve vaccine-induced antibody responses. Aims: Part I focuses on the adjuvant function of IFN-lambda blockade and aims to explore IL-28R antagonistic compounds (peptides, antibodies and small molecules) as novel adjuvants mediating enhanced antibody induction. Additionally, the immune-modulatory activity on macrophage, dendritic cells, and subsequent T- and B-cell activating effects will be examined. The impact of IL-28R blocking compounds will be evaluated in mouse models of influenza vaccination to demonstrate adjuvant efficacy in generating specific antibodies. Part II aims to explore the role of IFN-lambdas and SNPs on vaccine-induced antibody response (seroconversion and absolute titers) after trivalent non-adjuvanted influenza vaccine in a high-risk allogeneic haematopoietic stem cell transplant (HSCT) population. Hypotheses: Part I: Antagonistic compounds against the IL-28R block the IFN-lambda signalling and act as adjuvants in vitro and in vivo by mediating an increase in vaccine-induced antibody secretion. Part II: IL-28B SNPs affect the antibody production during vaccination of HSCT recipients. Rationale: This project carries high potential to (i) develop a novel tailored class of adjuvant in a highly translational setting; (ii) use IFN-lambda

modulating compounds to further comprehend the impact of IFN-lambdas signalling in vitro and in vivo; (iii) develop in detail a highly innovative approach to study vaccine responses possible impacting vaccination schedules in distinct populations based on the genotype background; (iv) form an international collaborative network with leading institutions to improve patient outcomes.

Keywords Polymorphism, Vaccine, Immunity, Interferon lambda, Adjuvant, IL28B, Infection
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