Journal of Vaccines & Vaccination
ISSN: 2157-7560

Mortensen and Dietrich, J Vaccines Vaccin 2016, 7:3
DOI: 10.4172/2157-7560.1000323

Short Communication Open Access

New Generation Combination Vaccines against *Streptococcus pyogenes*

Rasmus Mortensen and Jes Dietrich*

Department of Infectious Disease Immunology, Statens Serum Institut, Denmark

***Corresponding author:** Jes Dietrich, Department of Infectious Disease Immunology, Statens Serum Institut, Artillerivej 5, Copenhagen S, DK-2300, Denmark, Tel: +4532683819; E-mail: jdi@ssi.dk

Received date: May 19, 2016; **Accepted date:** May 20, 2016; **Published date:** May 24, 2016

Abstract

With our recent discovery of new protective non-M protein antigens expressed by *Streptococcus pyogenes*, as well as the characterization of GAS cellular and humoral immunity in human adults and children, we encourage the development of new combinational GAS vaccines, with the ability to induce Th1/Th17/IgG3 based memory immunity in humans.

Introduction

Group A streptococci (GAS; *Streptococcus pyogenes*) are major human pathogens causing both suppurative and non-suppurative infections. As a unique feature of these bacteria, infection with GAS can give rise to a remarkable variety of clinical conditions ranging from uncomplicated infections, such as pharyngitis and impetigo, to life threatening invasive diseases [1]. Despite decades of research, there are no licensed vaccines against GAS.

The majority of current vaccine strategies focus on induction of antibodies against the M protein. Fewer studies have considered conserved antigens or induction of GAS specific T cell responses. However, given the highly polymorphic nature of the M protein and the risk of inducing cross-reactive immune responses, vaccines based on conserved antigens have received increased focus over the past decade. Furthermore, the highly diverse spectrum of clinical manifestations of GAS, each of which involves differential expression of specific GAS genes (virulence factors etc.), argues for a vaccine strategy that combines several antigens to be fully protective. In support of this, it was recently reported that a combination of the M protein based J8 vaccine and an epitope of the Streptococcal IL-8 protease (SpyCEP), yielded protection against virulent GAS bacteria, to which the J8 vaccine itself had limited effect [2].

New non-M Protein Targets Identified by *in silico* or High Density Peptide Arrays Strategies

In a recent study we selected 21 antigens based on an *in silico* evaluation [3]. These were all upregulated in host-pathogen interaction studies and well conserved among different GAS strains. Among these, we selected antigens with both high cellular- and antibody responses in humans. Three antigens were shown for the first time to confer significant protection in a mouse intradermal infection model (spy0469, spy1228, spy1801) and therefore constitute promising vaccine candidates.

In the same study, we also introduced a high-density peptide array technology platform to identify linear B cell epitopes. One of the advantages with this technology is the impressive capacity, which enabled us to evaluate the IgG response of not only all putative proteins, but all putative epitopes in the entire M1 SF370 GAS genome (approx. 503.000 peptides in total). By detecting binding of human serum IgG on the array, we confirmed the antigenicity of the three protective antigens and located each of the recognized linear B cell epitopes. In addition, as much as 349 other proteins were recognized by serum IgG, including several antigens with published protective capacity (e.g. the M1 protein, Streptolysin O and the streptococcal C5a peptidase). Collectively the study showed that the immune response against GAS includes antibody as well as cellular responses against numerous different non-M protein antigens. Our results also demonstrated that the peptide array technology is indeed a very powerful screening tool for identifying new immunogenic antigens. Importantly, since the array technology provides detailed information about the epitope-pattern of all antigens, it allows for new generation GAS vaccines to be designed based exclusively on the immunogenic parts of the proteome.

Natural GAS Induced Th1/Th17/IgG3 Immunity; Using the Right Adjuvant

The development/refinement of effective and safe vaccines against GAS is dependent on knowledge about the immune response needed to combat the infection. There is ample evidence that antibodies develop after exposure to GAS bacteria. However, we showed recently that strong cellular Th1/Th17 immune responses are very frequent in humans as well [4]. T cells are essential in the class switching of antibody producing B cells. Accordingly, we observed that the humoral immunity was dominated by a Th1 associated phenotype of IgG1 and IgG3, which is known to be optimal for complement fixation. Interestingly, in the mouse model, we also observed a Th1/Th17 based immunity after GAS infection, and in line with other studies, our results show that local mucosal immunity is paramount for protection against intranasal infection (Mortensen et al, unpublished observations). The optimal immunization strategy against GAS should therefore induce both mucosal immunity to combat infections in the upper airway as well as systemic immunity to prevent spreading of bacteria that could lead to invasive GAS disease. Interestingly, a recent study from our lab showed that an immunization regimen involving a systemic prime (via subcutaneous vaccination using the adjuvant CAF01) and a subsequent 'pull' of the systemically primed cells with an intranasal booster vaccine (a so-called 'prime-pull' strategy) leads to

improved mucosal immunity over standard intranasal vaccination, while maintaining systemic immunity [5].

From this we suggest that 1) adjuvants such as aluminum hydroxide, known to induce Th2/IgG4 responses in humans, constitute a suboptimal adjuvant for a vaccine against GAS, compared to Th1/Th17 inducing adjuvants, and 2) vaccine strategies that induce systemic as well as local immunity, such as the prime-pull strategy, should be prioritized in future vaccination studies.

Future Subunit GAS Vaccines

To summarize, we propose that that future vaccines against GAS should induce systemic as well as local Th1/17 immunity combined with IgG3/IgA humoral immunity (by using a Th1/17 adjuvant such as CAF01 in a 'prime-pull' strategy). However, apart from constituting the optimal immunity to combat a GAS infection, this type of immunity could also pose potential safety challenges. Thus, as Th1 and Th17 have been implicated in the autoimmune process leading to the formation of heart lesions in rheumatic heart disease [6], any new vaccine candidate should be screened for sequence similarity to human proteins, and the T cells specific for the vaccine antigens should be tested for recognition of human heart proteins. Furthermore, complement activating antibodies, able to cross-react with heart antigens, have also been implicated in rheumatic heart disease. Based on this, it is important to test anti-sera directed against the vaccine candidate for cross-reactivity to human heart proteins. In fact, in our study we did observe that antibodies directed against spy1801 cross-reacted to a protein expressed in human heart valves [3]. This suggests that spy1801 should be further tested and highlights the importance of cross-reactivity analyses in the screening of new antigens.

To provide optimal protection and vaccine coverage, we finally propose that future GAS vaccines should be developed as combinational protein vaccines that include several protective antigens, such as spy1228 and spy0469. Additionally, numerous short linear epitopes, like the ones identified in our peptide array study, could also be combined in a vaccine construct to target a larger number of different GAS antigens. Importantly, we believe that the newly identified protective antigens, found in several labs, holds great promise for a GAS vaccine in the near future.

References

1. Cunningham MW (2000) Pathogenesis of group A streptococcal infections. Clin Microbiol Rev, 13: 470-511.
2. Pandey M, Langshaw E, Hartas J, Lam A, Batzloff MR, et al. (2015) A Synthetic M Protein Peptide Synergizes with a CXC Chemokine Protease To Induce Vaccine-Mediated Protection against Virulent Streptococcal Pyoderma and Bacteremia. J Immunol 194: 5915-5925.
3. Mortensen R, Nissen TN, Fredslund S, Rosenkrands I, Christensen JP, et al. (2016) Identifying protective Streptococcus pyogenes vaccine antigens recognized by both B and T cells in human adults and children. Sci Rep 6: 22030.
4. Mortensen R, Nissen TN, Blauenfeldt T, Christensen JP, Andersen P, et al. (2015) Adaptive Immunity against Streptococcus pyogenes in Adults Involves Increased IFN-gamma and IgG3 Responses Compared with Children. J Immunol 195: 1657-1664.
5. Christensen D, Mortensen R, Rosenkrands I, Dietrich J, Andersen P (2016) Vaccine-induced Th17 cells are established as resident memory cells in the lung and promote local IgA responses. Mucosal Immunol.
6. Guilherme L, Kalil J (2013) Rheumatic Heart Disease: Molecules Involved in Valve Tissue Inflammation Leading to the Autoimmune Process and Anti-S. pyogenes Vaccine. Frontiers in immunology 4: 352.