Biotechnology approaches to produce potent, self-adjuvanting antigen-adjuvant fusion protein subunit vaccines

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Biotechnology Approaches to Produce Potent, Self-Adjuvanting Antigen-Adjuvant Fusion Protein Subunit Vaccines

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Abstract
Traditional vaccination approaches (e.g. live attenuated or killed microorganisms) are among the most effective means to prevent the spread of infectious diseases. These approaches, nevertheless, have failed to yield successful vaccines against many important pathogens. To overcome this problem, methods have been developed to identify microbial components, against which protective immune responses can be elicited. Subunit antigens identified by these approaches enable the production of defined vaccines, with improved safety profiles. However, they are generally poorly immunogenic, necessitating their administration with potent immunostimulatory adjuvants. Since few safe and effective adjuvants are currently used in vaccines approved for human use, with those available displaying poor potency, or an inability to stimulate the types of immune responses required for vaccines against specific diseases (e.g. cytotoxic lymphocytes (CTLs) to treat cancers), the development of new vaccines will be aided by the availability of characterized platforms of new adjuvants, improving our capacity to rationally select adjuvants for different applications. One such approach, involves the addition of microbial components (pathogen-associated molecular patterns; PAMPs), that can stimulate strong immune responses, into subunit vaccine formulations. The conjugation of PAMPs to subunit antigens provides a means to greatly increase vaccine potency, by targeting immunostimulation and antigen to the same antigen presenting cell. Thus, methods that enable the efficient, and inexpensive production of antigen-adjuvant fusions represent a exciting means to improve immunity towards subunit antigens. Herein we review four protein-based adjuvants (flagellin, bacterial lipoproteins , the extra domain A of fibronectin (EDA), and heat shock proteins (Hsps)), which can be genetically fused to antigens to enable recombinant production of antigen-adjuvant fusion proteins, with a focus on their mechanisms of action, structural or sequence requirements for activity, sequence modifications to enhance their activity or simplify production, adverse effects, and examples of vaccines in preclinical or human clinical trials.

Keywords
Adjuvants; Extra domain A; Flagellin; Fusion proteins; Heat shock proteins; Lipopeptides; Subunit vaccines; Toll-like receptors; Vaccines

1. Introduction

Vaccines are preparations that are administered with the aim of stimulating immune responses that recognise and clear pathogens against which an individual has been immunized (Bobbala and Hook, 2016; Mak et al., 2014; Moyle and Toth, 2013). They represent, along with clean drinking water, the most effective means to prevent the spread of infectious diseases, and have been responsible for the eradication of smallpox in 1979 and the cattle virus Rinderpest in 2011 (Greenwood, 2014). However, despite the health benefits of vaccination, many important diseases remain without effective vaccines [e.g. dengue fever, lymphatic filariasis, acquired immune deficiency syndrome (AIDS), malaria, rheumatic heart