Review Paper

A Systemic Review on Bacillus Subtilis Spore Structure and Its Applications in the Development of Mucosal Vaccines and Adjuvants

Samira Ghaedmohammadi[1], Howra Bahrulolum[2], *Gholamreza Ahmadian[2]

1. Department of Cellular and Molecular Biology, Shiraz University, Estahban Higher Education Center, Estahban, Iran.
2. Institute of Industrial and Environmental Biotechnology, National Institute of Genetic Engineering and Biotechnology (NIGEB), Tehran, Iran.

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ABSTRACT

Background and Aim Surface display technology enables the binding of proteins and peptides to the surface of living cells, including mammalian cells, yeast, bacteria, and spores. Among the various systems used for surface display, Bacillus subtilis spores have advantages such as resistance to adverse environmental conditions such as heat, radiation and chemicals, safety for humans and no need for the heterologous protein to pass the membranes for binding to spores.

Methods & Materials This study is a review that investigates the structure of the Bacillus subtilis spore, spore surface display, and its application in the development of mucosal vaccines and adjuvants.

Ethical Considerations All Ethical principles in writing this article have been observed according to the instructions of the National Ethics Committee and the COPE regulations.

Results Heterologous proteins can be displayed genetically and non-genetically on the spore surface. The surface display is a promising strategy for the development of whole-cell factories with many industrial and biotechnological applications, leading to significant advances in the production of biocatalysts, the development of live vaccines, bio-adsorbents and sensors, epitope mapping, inhibitor design, and protein/peptide library screening.

Conclusion It is hoped that oral vaccines of Bacillus subtilis spores will be of significant help in the prevention and treatment of diseases including COVID-19 in the future.

Keywords:
Bacillus Subtilis, Spore, Surface Display

*** Corresponding Author:**
Gholamreza Ahmadian, PhD.
Address: Institute of Industrial and Environmental Biotechnology, National Institute of Genetic Engineering and Biotechnology (NIGEB), Tehran, Iran.
Tel: +98 (912) 4187608
E-mail: ahmadian@nigeb.ac.ir

Extended Abstract

Introduction

The surface display is a molecular technique, by which heterologous proteins are immobilized on the external surface of cells and has a wide range of applications, including the development of live vaccines, screening of peptide libraries, antibody production, whole-cell biocatalysts, and development of biosensors [1, 2]. Spore surface display technology, a method for anchoring functional proteins on the spore surface, is considered one of the most promising approaches to express heterologous proteins with high activity and stability and has several advantages. First, spores are resistant to harsh environmental conditions. Second, spores are made in the cytoplasm of bacterial cells; thus, the heterologous protein does not need to cross the cytoplasmic membrane to bind to the spore. Third, active molecular chaperones present in the cytoplasm of spore-producing bacteria can properly facilitate the proper secretion and expression of foreign heterologous proteins [11, 12]. The purpose of this study was to comprehensively review the use of Bacillus subtilis spores in the production of mucosal vaccines.

Materials and Methods

The present study was a systematic review, searching for articles using the keywords Bacillus subtilis spore, mucosal vaccine, and surface display, and their equivalent keywords in Persian, in Google Scholar, Scopus, and PubMed databases.

Results

The first case of genetic display on Bacillus subtilis spores was proposed in 2001 [1]. Since then, many heterologous proteins and enzymes have been successfully displayed on the surface of Bacillus subtilis spores, and most of them have used genetic methods to bind the target protein into one of the proteins of the spore coat or shell [25-30]. Although the genetic method has some advantages, such as no need to express and purify the target protein, the low level of expression or sometimes the absence of protein expression makes this method unsuitable for industrial applications. Another major problem in the genetic method is the release of living recombinant organisms in nature, which causes concern about the use of these genetically manipulated organisms [31]. To overcome these problems, a non-genetic approach has recently been proposed to use spores as a display system. The Gram-positive bacterium Bacillus subtilis has been widely studied as a prokaryotic system. This organism is not considered a pathogen and is classified as a probiotic for human and animal consumption. The mature Bacillus spore, once released from its mother cell, can survive for hundreds or even thousands of years in a metabolically inactive form [35]. On the other hand, the development of mucosal vaccines strongly relies on an efficient delivery system, and over the years, various approaches based on phages, bacteria, or artificial nanoparticles have been proposed to display and deliver antigens [36].

Discussion

The present study showed that mucosal spore-based vaccines have numerous advantages, such as helping mass vaccination by increasing ease and speed of delivery, reducing costs by eliminating purification steps, and flexible administration through mucosal and/or oral routes and thus providing vaccine delivery with needle-free and refrigeration-free systems [57]. Another unique feature of spore-based mucosal vaccines is that the spores have submicron-scale nanostructures that allow them to act as effective particulate adjuvants. Also, studies investigating the adjuvant properties of Bacillus subtilis spores show that strong adjuvant effects are observed when the spores are administered with protein antigens that are mixed or adsorbed on the surface of the spore coat. In addition, it has been found that the size of the spore particles is suitable for enhancing mucosal immunity. Thus, the flexibility of spores, together with a mucosal route of delivery, make spore vaccines a promising candidate, especially when mass production and large-scale vaccination are urgently needed [58].

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Initial idea design: Gholamreza Ahmadian; Study and research: Samira Ghaedmohammadi, Howra Bahrulolum; Author of the article: Samira Ghaedmohammadi, Howra Bahrulolum; Review: Gholamreza Ahmadian, Samira Ghaedmohammadi.

Conflicts of interest

The authors declare no conflict of intrest.