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Biotechnology and Its Applications in Vaccine Development

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ABSTRACT

Vaccine is a biological substance which stimulates the immune system by introducing a killed, weakened disease causing organism, or its surface protein in healthy body. The traditional vaccines are either killed microorganism or attenuated one to generate immune response in body after their inoculation. Biotechnology has revolutionized the field of biomedicines. Recombinant Hepatitis B surface antigen (HBsAg) was the first recombinant vaccine cloned and expressed in Saccharomyces cerevisiae and currently used as vaccine against HBV globally. Deoxyribonucleic acid (DNA) vaccines are basically genetically engineered DNA that when injected produce antigen and induce strong immune response. Messenger RNA (mRNA) vaccine, reverse vaccinology and reverse genetics platforms are utilized in variety development of vaccines and had shown promising results. Biotechnology has transformed the field of vaccinology and its utmost demand of time to put efforts in research to find cure for diseases for betterment of humankind.

Abbreviations: EBOV-GP: Ebola Virus Glycoprotein; FHBP: Factor H Binding Protein; NHBA: Neisseria Hairpin Binding Protein; NADA: Neisseria Adhesion A; DNA: Deoxyribonucleic Acid; mRNA: Messenger RNA; HBsAg: Hepatitis B Surface Antigen; EBOV-GP: Ebola Virus Glycoprotein

Introduction

Vaccine is a biological substance which stimulates the immune system by introducing a killed, weakened disease causing organism, or its surface protein in healthy body. Vaccines provide acquired immunity against a particular disease. The mode of action of vaccine is either prophylactic (to prevent the future infection) or it could be threptic specifically many cancer vaccines are under experimental stages [1, 2]. The term vaccine or vaccination derived from Variolae vaccinae (smallpox of the cow) was coined for the first time by an English Physician Edward Jenner to describe cow pox. He used the term in 1798 for his long experiments to establish protective role of cow pox against smallpox [3]. According to World Health Organization so far twenty-five (25) licensed vaccines are available for different infectious diseases [4]. The traditional vaccines are either killed microorganism or attenuated one to generate immune response in body after their inoculation. After emergence of Recombinant DNA Technology is a sub-field of Biotechnology remarkable positive impacts were observed on human health. From production of safe proteins, antibodies and gene therapy RDT revolutionized different aspects of biological studies [5].

Recombinant Sub-Unit Vaccine

After the discovery of gene cloning new doors were open in the field of therapeutics. It is a useful technique by cloning antigenic

protein (fragment) or its sub-type and clone it animal or other expression system to transcribe it. The purified expressed protein is administered in body to induce immune system [6]. Recombinant Hepatitis B surface antigen (HBsAg) was the first recombinant vaccine developed by Maurrice Hellmen and his team using cloning techniques. HBsAg was purified from serum of infected HBV carrier serum and then clone and expressed Saccharomyces cerevisiae (Baker,s Yeast). The HBsAg sub-type adw was expressed and purified from yeast culture. The vaccinated animals (monkeys, champzae and mice) were protected from disease after HBV adw and ady subtype challenge [7]. Human Papilloma Virus is DNA virus responsible to cause skin infections, warts and other sexually transmitted diseases. The envelope proteins E6 and E7 are the major oncogenic protein responsible to cause cervical squamous neoplasia [8]. HPV vaccine is also sub-unit vaccine composed of Virus Like Particles (VLPs) made from the major L protein of HPV that are expressed in Baculola Virus expression system. The VLPs provide immunity against HPV-16 and HPV-18 which are mainly responsible for cervical carcinoma in women. The HPV vaccines are FDA approved, first one Gardasil, is a quadrivalent vaccine and second is Cervarix, is a bivalent vaccine [9]. Neisseria Meningitidis is a rod-shaped gram-negative bacterium causing meningitis, meningococcemia and sepsis. It has thin extension on its surface called pilli which is used for attachment to host cell along with other virulence factors [10]. Broadly the vaccine for meningitis has been classified to two categories one is conjugate vaccine that contain polysaccharides from serotype W, C, A and Y while the other is recombinant vaccine providing immunity only against serotype B. The recombinant vaccine is comprised of four proteins i.e Por A, factor H binding protein (fHbp), Neisseria hairpin binding protein (NHBA), and Neisseria adhesion A (NadA) that provide immunity against serotype B [11,12].

Deoxyribonucleic Acid Vaccines

Deoxyribonucleic acid (DNA) vaccines are basically genetically engineered DNA that when injected produce antigen and induce strong immune response. The gene responsible for immunogenic response is identified, cloned and then expressed in host by directly injecting it. DNA vaccines have higher immune response inducing potential as compared to conventional live attenuated or killed vaccine [13]. In 1990 DNA vaccines were coined for the first time when plasmid DNA was injected in muscle or skin and induce immune response against viral along with non-viral antigens. DNA vaccines were thought to hold very promising future [14] but till date no DNA vaccine for humans has been approved by FDA only animal vaccines are available like canine melanoma [15], vaccine for West Nile Virus in horses [16].

Reverse Vaccinology

A new method in vaccinology which is the culmination of bioinformatics, genomics and proteomics to identify new genes in pathogen that could elicit immune response. This method was developed by Rino Rappuloi to make vaccine against serotype B meningococcus (MenB) [17]. The initial attempts for reverse vaccinology began with MenB vaccine development. MenB causes over 50% of meningococcal meningitis and no vaccine was available at time because of its exceptional structure. The bacterial polysaccharide is identical to human self-antigen, but surface protein greatly varies so it was very difficult to design vaccine. In order to achieve these 600 possible antigens were screened and expressed in E-coli. The most acceptable proteins were accepted for protype vaccine. Later on, lipopolysaccharide was used as adjuvant and enhanced immune response was acquired. The vaccine was declared effective and afe for humans. Furtherly, it has been used to develop vaccine for Streptococcus Pneumonia and antibiotic resistant staphylococcus Aureus. The major advantage of reerse vaccinology is it is cost effective and fast but only drawback is it only target proteins while conventional vaccinology also target other biomolecular components like polysaccharides [18].

Messenger RNA Vaccine

The role of messenger RNA (mRNA) in the cell is to synthesize protein (translation). In mRNA vaccine, the strand codes for disease specific proteins and are expressed on surface of cells. After expression of specific disease-causing antigen of cell surface the immune response is generated. mRNA vaccine is novel, safe and less expensive method as compared to conventional vaccines. The administration of mRNA vaccine remains a challenge for scientist because of stability and other pharmacological features.

There are three types of mRNA vaccines i.e,

Non-Replicating mRNA: The mRNA is injected in body where it is taken up by cells and express the antigen.

In-Vitro **Dendritic Cell Non-Replicating mRNA Vaccine:** Dendritic cells present antigen on its surface for other types of cells could produce immune response. In this type of mRNA vaccine dendrtic cells are extracted from patients and the transfected in vitro with antigen and injected back to patient to stimulate immune response.

In-Vivo **Self-Replicating mRNA:** In this strategy the pathogen mRNA is packed with additional mRNA to make sure it is copied inside cell [19].

Currently a great deal of research is in progress in filed of mRNA vaccine for cancer as well as infectious diseases. A study by Brazzoli et al describe self-amplifying mRNA vaccine encoding influenza virus Hemagglutinin protein. The vaccine elicits humoral and cellular immune response in mice [19]. The administration of mRNA encoding light and heaving chain of anti-HIV antibody encapsulated in nanoparticles from mice ven being challenged [20].

Reverse Genetics Platform

Reverse genetics literally means to understand the effect of gene by analyzing phenotypic effects of a specifically engineered gene sequences. Reverse genetics provide a low cost, effective and convenient method as compared to conventional approach for creating live attenuated vaccines. The common method to generate a live attenuated vaccine is to generate plasmids with sequences coding for structural and functional proteins. Influenza virus vaccine contains eight plasmids transfected tighter to produce vaccine [21]. The recent outbreaks of deadly Ebola virus accelerated the progress for its vaccine production. The vesicular stomatis virus-based vaccine is develop which is similar to reverse genetics. In this vaccine G protein of VSV replaced by Ebola Virus Glycoprotein (EBOV-GP) which is expressed on surface of VSV virus. The vaccine is now in phase three clinical trials [21].

Conclusion

Biotechnology has revolutionized the field of vaccinology and its utmost demand of time to put efforts in research to find cure for diseases for betterment of humankind.

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