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Bacterial Nanoparticle As a Vaccine for Meningococcal Disease

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Central nervous system infection, including viral or bacterial contamination is one of the main causes of disease and mortality. Kinds of vaccines to prevent infectious diseases are produced. These vaccines are usually produced by external or internal microbial components. These components are usually made from a combination of proteins and carbohydrates, proteins or lipid. The bacteria is Types of pathogenic microbes that are considered capable of causing disease and potential use as antigens manufacturer to provider or transfer of vaccine. Bacteria contain the various components such as a cell wall, outer membrane, lipopolysaccharides and the flagella, which all components has antigenic properties and stimulates the immune response. Utilize of outer membrane vesicles(OMV) is one of the newest and affordable cases.OMV as a nanometer proteoliposome particle germinates through potential growth. OMV also increase the immunogenic protein antigen without adding the adjuvant. OMV product via two pathways: 1) Recruiting of meningococcal bacteria that grow in a specific environment, 2) Transfer surface antigens to virus like particle in order to express surface antigen.Problem in the meningococcal bacteria presence of endotoxin and need a detoxified but in virus-like particle system does not have this issue because of endotoxin is absent, Instead there are limitation in gene transfer. One of the most studied bacteria that produces vesicles bacterium is *Escherichia coli*. Since the whole genome of *E.coli* bacteria could be detected and with genetic engineering of bacteria could be add antigens, and these antigens could be cloned. OMV expression genes that induce immunity against cell surface antigens result to the immune response against diseases such as typhoid fever and meningococcal disease.

Keyword: polyvalent vaccine, Bacterial meningitis, outer membrane vesicles.

During its evolution, bacteria have learned how to compete eukaryotic cells, proliferation and survival in the environment or the host cell. Pathogenicity of these bacteria results from effects of the interaction these organisms with immune system. Secretion of Homo-serine lactone as extracellular protein, regulate the gene expression in bacterial populations[1]. However, this mechanism is highly efficient because these protein Exposure to rapid dilution and possible degradation by host cell proteases. OMV is an alternative cell to cell communication among bacteria has recently been proposed. OMV produced by the outer membrane of gram negative bacteria can transmission of signal, transfer of DNA and proteins[2]. OMV has been used as a vector for vaccines and may also be used as drug carriers[3]. OMV produce may be due to a local increase in Periplasmic protein or lack of connection with the peptidoglycan layer[4]. For further OMV product, chemical and mechanical methods can be used to destroy Gram-negative bacteria[5]. Add or removing subunit proteins associated with the membrane could be formed due to the higher OMV formation that causes less stable membrane. One of important factor is the Tol-Pal system, a multi-protein complex that makes up the bridge between the outer membrane and the peptidoglycan[6].

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bacterium such *Pseudomonas aeruginosa*[11]. Stress can trigger the release of large amounts of vesicles from the *Pseudomonas aeruginosa*, the synthesis of 2-heptyl-3-hydroxy-4-quinolone (PQS) stimulation of omv production , this indicated that OMV production which is a regulatory factor rather

Table 1. Crucial name of protein or gene expression of outer membrane vesicles

Name of protein or Gene	Target	References
degP	Removing it causes the more formation of outer membrane vesicles	McBroom AJ et al.[7]
egS	Removing it causes the more formation of outer membrane vesicles	McBroom AJ et al.[7]
fliC	Removing it causes the decrease formation of outer membrane vesicles	Manabe T et al.[8]
flgK	Removing it causes the decrease formation of outer membrane vesicles	Manabe T et al.[8]
rmpM	Removing it causes the more formation of outer membrane vesicles	van de Waterbeemd B et al.[9]
Tol-Pal	Removing each subunit causes the more formation of outer membrane vesicles	van de Waterbeemd B et al.[9]

than to be a factor generated during stress[12]. PQS with hydrophobic properties can binds to the 4×phosphate acyl chain from LPS, this interaction causes a flip-flop effect on the membrane and thus the outer layer surrounding the inner layer, when the area is large enough the membranes in response to this mismatch resulting to membrane budding and detachment the part of membrane and formation of OMV[12]. Due to separation and loss associated the outer membrane with the cell wall and underlying lipid, vesicles formation produced by the presence of lipid[4]. Geometric analysis of these vesicles with two-dimensional (2D) and Three-dimensional (3D) have shown that these vesicles are not stable in the size[13]. IN some bacteria shown that the OMV can transfer the fragment of DNA and plasmid[10]. DNA transfer with OMV in Ruminococcus bacteria has been found to help cause Cellulitis in strains that lacking these genes[14].

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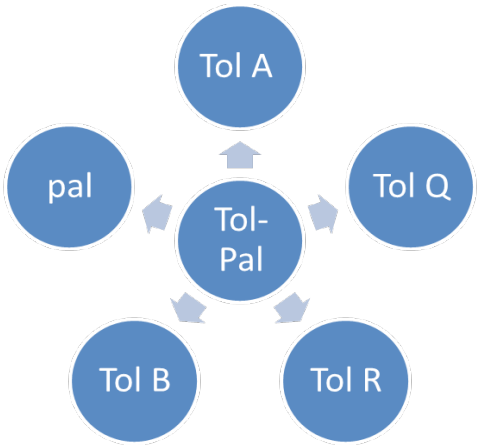
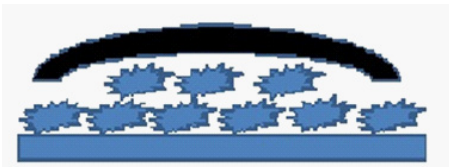
OMV structure as a source of antigen presentation has advantage such as OMV surface antigen retains its physicochemical property. Using vesicles containing Escherichia coli ClyA and fusion antigen with ClyA result in different activities[21]. In The *E.coli* OMV is rich with ClyA, a bacterial hemolysin protein. ClyA is a toxin that causes a gap (pore) on the cell membrane and produced by invasive strain of *Escherichia coli*. To add other units including foreign antigens to OMV, they can be connected to the ClyA. It was also observed that the presence of ClyA merged

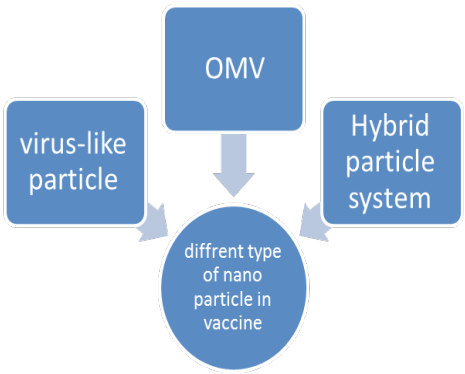
into OMV is dependent on oxidative status[21, 22]. OMV can affected with genetic engineering and with the aid of ClyA as the donor have different antigens on their surface. Other studies with recombinant Salmonella-containing OMV with Leishmania antigen shown the foreign antigen



Pic. 1. TOl-Pal system and subunit" Presence of this subunit help the bacterial envelope stability by binding the outer membrane and cytoplasmic membrane to peptidoglycan



Pic. 2. View of outer membrane vesicle formation in the model with increasing units of peptidoglycan



Pic. 3. Types of nano-particles used for vaccine

was detected in the outer membrane of bacterial cell[23]. To produce and isolated vesicles, detergents such as deoxycolate or EDTA chelating element can used[24] with destruction of the cell membrane, the vesicles is formed and release , Finally with the ultracentrifuge OMV can be absorbed into the precipitation of aluminum hydroxide.

OMV and Meningococcal

Neisseria meningitidis serogroup B causes most of bacterial meningitis in adults[25]. Ivo Claassen et al. examining vaccines produced using genetically modified of two strains of serogroup B, this strains express class 1of outer membrane proteins that contain two proteins PorA and OMP. Finally, with the aid of deoxycolate the OMV extracted and aluminum phosphate as an adjuvant was used. It was found that the vaccine is safe for humans and can also cause an immune response in mice[26-28]. Capsular polysaccharide of Group B first option for vaccine, but unfortunately do not have an immunity[29]. After the culture in medium containing L - glutamate, L - cysteine, glucose, yeast extracts, incubated for 18 hours at a temperature of 36 ° C. Continuing with deoxycolate bacteria lysis and with the centrifuge carcass bacteria sedimented, in this case, OMV remains in the supernatant[30]. One problem with this method is the possible presence of endotoxin vaccine is that it examines with the extent Limulus methods. OMV vaccines combined with fivefold of Limulus lysate and will be kept for 45 minutes at 37 ° C, clotting Limulus lysate with lipid A indicative the presence of endotoxin. Activity these endotoxins are compared with *Escherichia coli* endotoxin[31]. Modern methods for removing endotoxins are use of mutants that are genetically have detoxified LPS, Also the mutant with more expression in the proteins, such as POrA can used[32]. Polysaccharide group B, N - acetyl Neuraminic acid that autoantigen. Today Polyvalent OMV vaccine for serogroups A, W, Y are generated and the first phase is over now[33, 34].

OMV and its interaction with the immune system

OMV such parent bacteria cell has interaction with the immune system and important factor to producing inflammation[35]. Outer membrane vesicle components including LPS and purines a part of complex heterogeneity that presented to pathogen-associated molecular patterns (PAMP) the first line of innate immune response. OMV

has more potential than LPS in stimulating the immune system, in the result nanoparticles play an essential role in the immune stimulation[36]. Using different OMV bacteria, immune response produce antibodies against antigenic complex in the vesicle[37]. Observed that OMV can be effectively induce humeral and mucosal immune response without requires the pathogens components[18].

Discussion and conclusions

Outer membrane vesicles are compounds that are released by the bacteria into the environment and transfer material such as DNA, proteins, toxins, etc. Producing OMV in bacterial culture and isolation this compound can be used as an inexpensive and effective vaccine. Finally with transfer other bacterial surface antigens into conjugated plasmid and integrated into bacteria can produced polyvalent vaccines. The benefits of this vaccine is cost, ease of preparation and processing, integrating multiple polyvalent vaccine a single vaccine and less need for booster. Other methods that have act similar outer membrane vesicles such: virus-like particles and hybrid particle systems can be used[38].

Disadvantages of hybrid Particle systems is the limit of mentioned antigens used , to produce this particles use polymers such as poly acetic acid, liposomes and simple lipid emulsion[39]. The disadvantages of using virus-like particles can limit the manipulation of these particles as a carrier (These particles have a limited ability to carry). The benefits of these particles referred to a simple biological structure. Due to the presence of low but steady release of vesicles in vivo and bacterial antigens, which now contain foreign antigens the stimulate the immune system over time and an acceptable level of antibodies will be present in the body for long time.

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