Mini Review

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2022.42.006752

Review on *Fusobacterium necrophorum* Putative Candidates for Vaccine Development Strategies: Outer Membrane Proteins and Outer Membrane Vesicles

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ARTICLE INFO

Received: March 03, 2022

Published: March 09, 2022

Citation: Prabha K Bista, Deepti Pillai, Sanjeev K Narayanan. Review on *Fusobacterium necrophorum* Putative Candidates for Vaccine Development Strategies: Outer Membrane Proteins and Outer Membrane Vesicles. Biomed J Sci & Tech Res 42(3)-2022. BJSTR. MS.ID.006752.

Keywords: *Fusobacterium Necrophorum*; Liver Abscess, Outer Membrane Proteins (OMPS); Outer Membrane Vesicles (OMVS); And Vaccine Candidates

ABSTRACT

Fusobacterium necrophorum is a Gram-negative, strictly anaerobic bacterium associated with necrotic infections in animals and humans. The bacterium is an opportunistic and primary pathogen that causes liver abscess, footrot, and laryngeal infections in cattle. Liver abscess in cattle is reported at 20.7% annually, leading to liver condemnation and economic burden to the feedlot industry. Antibiotics are the mainstay for treatment; however, the reports of antibiotic resistance and demand for antibiotic-free, natural and organic beef have demanded alternative therapies and preventatives. Hence, developing an effective vaccine is essential to control infections and economic loss to the cattle industry. Currently, there is no licensed vaccine to prevent liver abscesses in cattle. A number of virulence factors for *F. necrophorum* have been explored in the past for vaccine development. Each one has some advantages and disadvantages concerning immunogenicity and protective effect. The review summarizes vaccine candidates explored in the past, mainly focusing on *F. necrophorum*. The review also connects some concepts related to virulence factors found in *F. necrophorum* and how it could be a promising vaccine candidate based on the studies done in other Gram-negatives.

Mini Review

Fusobacterium necrophorum, a Gram-negative anaerobic bacillus, is an opportunistic pathogen isolated from oral cavities, gastrointestinal and genitourinary tracts of humans and animals [1,2]. The bacterium is associated with Lemierre's syndrome affecting young and healthy individuals and necrotic infections in hepatic, abdominal, and respiratory organs in animals [3,4]. The bacteria are primary causative agents of liver abscess, foot rot, and calf diphtheria, sometimes in mixed infections with other bacteria such as *Trueperella pyogenes* and *Porphyromonas* species [5,6]. *F. necrophorum* has been classified into four biotypes: A, B, AB, and C [7]. Biotypes A and B are of veterinary importance and associated with cattle liver abscesses. Biotype A, subspecies *necrophorum*, and Biotype B, subspecies *funduliforme*, vary in cell morphology, colony characteristics, virulence capacity, virulence factors, 16s rRNA sequences, and DNA gyrase B subunit [7,8]. The subspecies *necrophorum* is more virulent and frequently isolated than the subspecies *funduliforme,* and is the primary causative agent in liver abscesses [9]. Annually, the rate of incidence of liver abscess in feedlot cattle is 10-20% [10].

Generally, the incidence is higher in cattle fed with high grain-based diets where the progression occurs from chronic acidosis and rumenitis to liver abscess [11]. The National Beef Quality

Report 2016 has reported a liver abscess rate of 20.7%, causing liver condemnation [12]. Thus, this infection and search for a cure have been of economic importance in the feedlot industry. So far, the antibiotics such as tylosin-phosphate and virginiamycin have been approved as antimicrobial feed additives to control liver abscesses [13]. More generally, with the potential threat of antimicrobial resistance [14], new approaches and preventive strategies are needed, including vaccination. There is no successful vaccine against *F. necrophorum*, which has pointed out the need to investigate different vaccine candidates. This mini-review provides an overview of different vaccine candidates investigated in the past and other virulence factors that could be explored as a promising target for a vaccine.

Lipopolysaccharide (LPS) and Hemagglutinin

F. necrophorum has several virulence factors, including leukotoxin, lipopolysaccharides (LPS), hemolysin, hemagglutinin, outer membrane adhesins, extracellular proteases, and other enzymes. [1,9,15-17]. Currently, the focus has been looking into proteins as vaccine candidates, mainly surface proteins (LPS), membrane proteins (OMPs and OMVs), and secreted proteins (hemolysins).

F. necrophorum lipopolysaccharide and hemagglutinin plays a crucial role in disease pathogenesis. LPS can induce endothelial cell injury, toxic hepatitis and has anti-phagocytic property, thus indicating its role in eliciting an immune response [18,19]. Similarly, haemagglutinin of *F. necrophorum* has the ability to agglutinate chicken, human RBCs, and bovine platelets. Kanoe and Yamanaka reported that antisera specific for hemagglutinin reduced bacterial adherence and platelets aggregation, indicating the role of haemagglutinin in the bacterial attachment during the initial stages of abscess formation [20,21]. However, the protective functions of LPS and hemagglutinin have not been reported.

Exotoxins: Hemolysin and Leukotoxin

Leukotoxins are critical virulence factors involved in the pathogenesis of anaerobic infection. In *F. necrophorum*, leukotoxin plays a significant role in the pathogenesis of bovine liver abscesses. Its production is directly proportional to the severity of abscesses in cattle [22]. Leukotoxin induces cellular activation and apoptosis of bovine leukocytes for inflammation modulation [15]. Studies have demonstrated that recombinant leukotoxoid challenge in a mouse model induced good immune protection [1].

Similarly, another virulence factor that has a role in the pathogenesis of *F. necrophorum* is hemolysin. Iron acquisition is required for bacterial colonization and is critical for invasive infections such as liver abscess. Studies show that the production of hemolysin helps in successful colonization of *F. necrophorum* during infection by iron acquisition mechanism- a key role in pathogenesis [23].

The fact about the co-existence of *F. necrophorum* with T. *pyogenes* in liver abscesses in cattle is well documented in the literature. This symbiotic relation is mediated through pathogenic synergy between these two pathogens where T. *pyogenes* creates an anaerobic environment for the initial establishment of *F. necrophorum*. In turn, *F. necrophorum* produces leukotoxin to protect T. *pyogenes* from phagocytosis [24]. A study was conducted to examine the combination of leukotoxoids of *F. necrophorum* and bacterin of *T. pyogenes* [25]. However, the vaccine was only effective in low prevalence settings because of the biases related to the pen effect and antibiotics effect on recurrent infections in the studied group.

T. pyogenes is also found in mixed infections with other anaerobes such as *Clostridium perfringens*. A study conducted in a mouse model showed that pyolysin of *T. pyogenes* and phospholipase C of *Clostridium perfringens*, when used in combination, was effective in immuno-protection and reduced infections in mice challenged with *T. pyogenes* or *Clostridium perfringens* [26–28]. Based on the studies mentioned above, evaluating pyolysin and leukotoxin/ hemolysin combinations would be a possible combination to explore.

Outer Membrane Proteins (OMP)

OMPs of Gram-negative bacteria serve as a barrier for any toxic materials entering the bacterial cell. The OMPs are associated with host-bacteria interaction, adhesion, and induction of protective immunity [29]. Like other Gram-negative bacteria, the primary infection in *F. necrophorum* commences by attachment to the epithelial and endothelial cells of the liver and ruminal wall [17, 30] The attachment is facilitated by different adhesins and toxins, causing colonization and establishment in the liver parenchyma to cause an abscess [9,31]. Studies show that after the rumen entry, *F. necrophorum* enters through aggravated regions of the ruminal surface and enters portal circulation. Once trapped in the liver, it causes abscesses [11]. The OMPs of *F. necrophorum* facilitate direct interactions with the host and likely contain important constituents involved during infection, transmission, and survival, including putative vaccine candidates [17,32]. Therefore, a multivalent vaccine including OMPs and leukotoxin has been proposed in the past.

Previous studies identified adhesins that could have a potential role in the attachment of *F. necrophorum* to the host cells. Kumar et al., 2013 identified four adhesins (17kDa, 24kDa, 40kDa, and 74kDa) with high binding affinity to bovine adrenal gland endothelial cell line (EJG), *in-vitro*. Later, one of these adhesins was characterized as 42.4 kDa OMP FomA. [32]. FomA has been characterized in *F.*

nucleatum and *F. periodonticum* as well. Based on the N-terminal sequences, FomA protein in *F. necrophorum* has 96% homology with FomA of *F. nucleatum* [32]. This protein is immunogenic and plays a role in the attachment of bacteria to the host cells [33]. The FomA protein in *F. nucleatum* is TLR2 and voltage-dependent porin [34]. FomA is involved in NF-kB, regulating genes responsible for host immune response. The activation of NF-kB is through TLR2 dependent fashion [35], thus indicating FomA could trigger host immune response. These studies suggest that FomA could be a potential vaccine candidate for controlling *F. necrophorum* infections. However, detailed research on the mechanism of action and receptors is necessary to understand the virulence mechanism of FomA in *F. necrophorum*.

FadA (13.6 kDa) is another membrane protein extensively studied for its role in the adhesion, invasion, and colonization of *F. nucleatum* in the host body [36,37]. FadA interacts with the vascular endothelial cadherin causing endothelial impermeability to allow the bacteria to cross through the tight junction of endothelium and proliferate to cause infections [38]. Moreover, many studies have suggested FadA adhesion is significant in inducing inflammation and suppressing host immunity by modulating the E-cadherin/ß-catenin pathway leading to colorectal cancer (CRC) [39].

OmpA and OmpH Family Protein

OmpA is studied for its membrane-associated pathogenicity and biofilm formation in Gram-negative bacteria [40,41]. OmpA family proteins are attached to peptidoglycan layer (via diaminopimelic acid) with the conserved domain at the C terminus. [42]. These proteins are known for their role at different stages during infections, such as interfering with the complement system, adhesion to the host cell, and mediating biofilm formation in several Gram-negative pathogens such as *Pseudomonas, Escherichia coli, and Acinetobacter baumannii* [43]. OmpA also helps in the intracellular survival of bacterial pathogens [44–47].

OmpH, a structural component of OMP in Gram-negative bacteria, is closely related to the family of porins [48]. Immune efficacy of OmpH based vaccines preparation has been studied in bacterial species such as *Pasteurella multocida*. The OmpH based vaccine has been used for protecting swamp buffaloes from hemorrhagic septicemia in South Asian countries. [49]. OmpH has other functions as well such as in *Pseudomonas aeruginosa*, it provides stability to the outer membrane through interaction with lipopolysaccharide [50].

Hence, exploring and identifying these different OMP family proteins in *F. necrophorum* and their role in adhesion and inducing protective immunity during liver abscesses in cattle could be exploited to study their protective function and vaccine potential.

Outer Membrane Vesicles (OMVs)

Outer membrane vesicles (OMVs) are spherical, membrane-enclosed nanostructures released during bacterial growth. These nanostructures are composed of periplasmic proteins, toxins and sometimes genetic materials [51]. The OMVs play an important role in transporting toxins into the host cell and modulating the host immune reponse [51,52]. Therefore, OMVs, as efficient vaccine candidates, have received significant attention. In most cases, OMVs are shown to positively minimize infections in animal models [53,54]. The OMV based vaccine is successfully approved for *Neisseria meningitidis* and is currently the only licensed vaccine in humans [55,56]. OMV has also been studied as a targeted drug delivery vehicle and vaccine adjuvants [57,58]. OMVs are identified in *Fusobacterium* species, including *F. nucleatum* [59]. The OMVs of *F. nucleatum* have modulated the innate immune response by promoting inflammation [35,60]. Based on the proteomics analysis, OMPs serve as the significant components of OMVs.

Conclusion

OMPs and OMVs could be potential vaccine candidates to control *F. necrophorum* infections in cattle based on the virulence and immunomodulatory role observed in different bacterial species, including *Fusobacterium* species. Therefore, identifying and characterizing these OMPs and OMV components in *F. necrophorum* could widen the area to explore and develop an effective vaccine.

Funding

The work was supported by the Department of Comparative Pathobiology, College of Veterinary Medicine, Purdue University (USA).

Conflict of Interest

The authors declare no conflict of interest.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2022.42.006752

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