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Mucosal and systemic responses of immunogenic vaccines candidates against enteric *Escherichia coli* infections in ruminants: A review

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ABSTRACT

Innumerable *Escherichia coli* of animal origin are identified, which are of economic significance, likewise, cattle, sheep and goats are the carrier of enterohaemorrhagic *E. coli*, which are less pathogenic, and can spread to people by way of direct contact and through the contamination of foodstuff or portable drinking water, causing serious illness. The immunization of ruminants has been carried out for ages and is largely acknowledged as the most economical and maintainable process of monitoring *E. coli* infection in ruminants. Yet, only a limited number of *E. coli* vaccines are obtainable. Mucosal surfaces are the most important ingress for *E. coli* and thus mucosal immune responses function as the primary means of fortification. Largely contemporary vaccination processes are done by parenteral administration and merely limited number of *E. coli* vaccines are inoculated via mucosal itinerary, due to its decreased efficacy. Nevertheless, aiming at maximal mucosal partitions to stimulate defensive immunity at both mucosal compartments and systemic site epitomises a prodigious task. Enormous determinations are involved in order to improve on novel mucosal *E. coli* vaccines candidate by choosing apposite antigens with potent immunogenicity, manipulating novel mucosal itineraries of inoculation and choosing immune-inducing adjuvants. The target of *E. coli* mucosal vaccines is to stimulate a comprehensive, effective and defensive immunity by specifically counteracting the antibodies at mucosal linings and by the stimulation of cellular immunity. Furthermore, effective *E. coli* mucosal vaccine would make vaccination measures stress-free and appropriate for large number of inoculation. On account of contemporary advancement in proteomics, metagenomics, metabolomics and transcriptomics research, a comprehensive appraisal of the immeasurable genes and proteins that were divulged by a bacterium is now in easy reach. Moreover, there exist marvellous prospects in this bourgeoning technologies in comprehending the host bacteria affiliation. Accordingly, the flourishing knowledge could massively guarantee to the progression of immunogenic vaccines against *E. coli* infections in both humans and animals. This review highlight and expounds on the current prominence of mucosal and systemic immunogenic vaccines for the prevention of *E. coli* infections in ruminants.

1. Introduction

Escherichia coli of ruminants that are pathogenic predominantly fit in to the septicaemic *E. coli* (SePEC), diarrhoeagenic *E. coli* (DEC), uropathogenic *E. coli* (UPEC) and the mammary-pathogenic *E. coli* (MPEC). The diarrhoeagenic *E. coli* can be additionally classified into the enterotoxigenic *E. coli* (ETEC) liberating enterotoxins that causes hypersecretion of electrolytes and water by enterocytes in ruminants

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and the enteropathogenic *E. coli* (EPEC) which produces attachment and effacing (AE) lesions in mammals. Ruminants that release Shiga toxin (STx) and AE lesions cause subclinical infections [1]. The strains are also called enterohaemorrhagic *E. coli* or EHEC and can cause serious illness in humans, predominantly elderly and children [2,3]. Albeit numerous *E. coli* of animal origin existing, there is still a few mucosal vaccines of *E. coli* against ruminants. Animals that are excreting in superfluous of 10^4 c.f.u. g/faeces and divulge the terminal rectal occupation as formerly detected [4], could be immunized to avert super excretion using vaccines comprising of EHEC type III secreted proteins, such as locus of enterocyte effacement-4 (LEE4) which are in the offing to avert cattle-to-cattle spread and safeguard human health [4].

The features of numerous vaccine-adjuvant preparations that have ability of stimulating both systemic and mucosal immunity following intradermal inoculation showed that skin dendritic cells may function as potent antigen presenting cells for the stimulation of mucosal immune responses, if the conditions of microenvironment are suitably handled following the induction antigen. Potent mucosal adjuvants, as well as bacteriological toxins, chemical enhancers of cyclic AMP, and vitamin D3, all have common capability to stimulate dendritic cell relocation from the skin to Peyer's patches following antigen stimulated development [5].

The epithelial coating of mucus membranes in ruminants is wide-ranging and of very large dimension. Mucosal linings are largely embodied by the respiratory, the gastrointestinal and the urogenital tracts and hence are susceptible to be infected by *E. coli*. Mucosal linings are safeguarded from exterior assaults by physical and chemical protective mechanisms, innate and adaptive mucosal immune systems are able to discern *E. coli* that move into the system through the mucosal linings from those presented through the circulation. The mucosal immune system is predominantly partitioned into inductive and effector compartments. *E. coli* on mucosal linings are trapped either on association with antigen-presenting dendritic cells (APCs), or through the M cell and by stimulating analogous T and B lymphocytes [6]. Epithelial barricades on mucosal linings at dissimilar locations vary in their cellular structure, and antigen at different mucosal sites are modified according to their structure. Multiple layered squamous epithelia cover the oral cavity, pharynx, esophagus and urethra while the intestinal mucosa is protected by one cell layer, and the airway and rectal surface differs from pseudo-stratified to simple epithelium. These dissimilar epithelia are not impassable barricades, but somewhat are cell combinations that control passages between the lumen and the lamina propria. In stratified and pseudo-stratified epithelia, antigen processing dendritic cells move into the epithelium, obtain antigens, and rove back into the local or distant structured lymphoid tissues. In simple intestinal and airway epithelia whose intercellular spaces are sealed by tight junctions, specific epithelial M cells deliver antigen through transepithelial conveyance from the lumen to structured lymphoid tissues located in the mucosa [7,8].

These days, the enormous mainstream of approved veterinary immunogenic vaccines are the live attenuated, killed or inactivated bacteria, cell membrane components or toxoids [9,10]. Live attenuated immunogenic vaccines are very potent because they stimulate both cellular and humoral immune responses [11,12]. Nevertheless, the main apprehension that is connected with these types of vaccines is the impending danger of relapse of the bacteria for a more virulent phenotype [10,13]. Killed or inactivated vaccines are characteristically innocuous; nevertheless, they may perchance be less potent than the attenuated vaccines. The commercial vaccines of the inactivated toxin types have some downsides since they needed some multifaceted constituents in culture medium. The drawbacks of these vaccine forms and the failure of numerous diseases to be treated efficaciously with a potent vaccine necessitates the need for an improved and innocuous vaccine that can avert, control or wipe out animal diseases [14,15]. Recombinant vaccines epitomise a gorgeous approach by which the downsides of conventional vaccines can be overwhelmed, and a number of sub-unit vaccines are now obtainable at the veterinary segment. Determinations of developing more potent vaccines against *E. coli* using recombinant DNA technology is in progression around the globe. Recombinant vaccines are developed based on recombinant highly purified antigens via structure-based strategy, epitopes highlighting or genomic-based selection [16]. In addition to improving the comprehension of the genes accountable for virulence and enabling the identification of the determinants of defensive immune responses, these molecular methods have provided new procedures of developing novel vaccines against *E.coli*. Nonetheless, the intrinsic immunogenicity of recombinant antigens is repeatedly low in contrast to the more traditional vaccines, and there is a need for a more potent and innocuous vaccine adjuvants to guarantee that recombinant vaccines can thrive. The low immunogenicity recurrently observed in recombinant antigens occurs due to a lack of exogenous immune activating components. Recombinant antigens can be obtainable in dissimilar adjuvants, and the immunomodulatory effects are dependent upon the particular adjuvant used in conjunction with specific antigens. Therefore, this review focuses and expounds on the conventional, contemporary approaches comprising of proteomics, metagenomics, transcriptomics, metabolomics technique and their prominence on mucosal and systemic immunogenic vaccines for the prevention of *E. coli* infections in ruminants.

1.1. Vaccines against enterotoxigenic E. coli

In humans and sheep intestinal infections with enterotoxigenic *E. coli* (ETEC) is widespread. A very high mortality due to severe diarrhoea was observed in calves and lambs with ETEC infections in the first four days of life [17]. ETEC possesses long attachments or fimbriae on their exterior, which permits them to attach to particular receptors on small intestinal enterocytes and inhabit the small intestine. This is the early phase in the setting up of the enteric infection and the fimbriae is connected with ETEC strains that are responsible for initiating diarrhoea [17]. Usually F5, F7 and F17 fimbriae are predominantly recognised in calves [18]. Additionally, F5 and F41 fimbriae producing ETEC have been identified in lambs [17].

ETEC outbreaks F5, F41 and F17 were identified in young ruminants. Four dissimilar antigenic variants of the main subunit of F17 have been recognized, specifically F17a (FY or Att25), F17b (F17-like, Vir adhesin), F17c (20K, G) and F17d (Att111 or F111). F17a and F17d are found in bovine ETEC strains, F17b on septicaemic *E. coli* in calves and lambs and F17c on *E. coli* in calves with diarrhoea or septicaemia, lambs with nephrosis or septicaemia, kids with septicaemia and humans with urinary tract infections [19]. The adhesin of F17 fimbriae is the F17G protein. So far only two variants of the f17G gene have been distinguished by PCR, f17GI, connected primarily with F17a and F17d, and f17GII, linked largely with F17band F17c fimbriae although modifications in receptor affinity of the adhesin protein, have been detected for all F17 variants [17].

After infection, ETEC release enterotoxins which induces serious squelchy diarrhoea by upsetting the electrolyte and water balance in the intestine [17]. These enterotoxins comprise human heat-stable toxin a (StaP or STaH), heat-labile toxin (LT), enteroaggregative heat-stable toxin 1 (EAST1) and heat-stable toxin b (STb). In ruminants ETEC isolates largely release StaP, rarely LT or STb are recognized [18,20]. EAST1 is not predominant in bovine ETEC, but very much related with the adhesin CS31, which is predominant in isolates from calves with *E. coli* septicaemia [17].

Overall, large number of infections in young ruminants can be averted by passive colostral and lactogenic immunity acquired by immunization of dams [17]. Conversely, as ETEC infections are non-invasive gastrointestinal infections, mucosal, i.e. lactogenic immunity rather than systemic thus, colostral immunity will be essential to fight the illness. Both comprise inactivated microorganisms with fimbriae or purified fimbriae with or without LT toxoid and are administered