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Review

Advances in vaccination against avian pathogenic *Escherichia coli* respiratory disease: Potentials and limitations

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ABSTRACT

Avian pathogenic *Escherichia coli* (APEC) is one of the most economically devastating pathogens affecting the poultry industry. This group of extra-intestinal *E. coli* causes a variety of clinical conditions including airsacculitis and cellulitis. The economic impact of APEC is mainly due to mortality, slower growth rates, and carcass downgrading. In commercial broiler operations, APEC infections are controlled indirectly by vaccination against other respiratory diseases and minimizing stress conditions, and directly by administration of antimicrobial agents to suppress the infection in already infected flocks. The fact that most APEC strains possess some common virulence factors suggests that an effective vaccine against APEC is a viable option. The most important virulence factors that have been investigated over the years include type I and P fimbriae, aerobactin iron-acquisition system, and serum resistance traits. Despite the potential for developing an efficacious vaccine to combat this economically important poultry disease, several obstacles hinder such efforts. Those obstacles include the cost, vaccine delivery method and timing of vaccination as the birds should be immune to APEC by 21 days of age. Herein, we review the various attempts to develop an effective vaccine against the respiratory form of APEC diseases in poultry. We also discuss in-depth the potentials and limitations of such vaccines.

Contents

Abbreviations: APEC, avian pathogenic *Escherichia coli*; *iss*, increased serum resistance gene; CFU, colony forming units; SC, subcutaneous; Intravenous: IM, intramuscular; IP, intraperitonial; IT, intratracheal; IROMP, iron regulated outer membrane protein; SRP, siderophore receptor protein; *cya*, adenyl cyclase; *crp*, cyclic adenosine 3′,5′-monophosphate (cAMP) receptor protein.

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1. Introduction

Avian pathogenic *Escherichia coli* (APEC) is a group of *E. coli* that causes a variety of extra-intestinal diseases in chickens, turkeys, and other avian species. In fact, APEC is the most common bacterial pathogen affecting chickens, which costs the poultry industry hundreds of millions of dollars in economic losses worldwide (Barnes et al., 2008). Although APEC causes a variety of extraintestinal diseases in poultry, colibacillosis, airsacculitis/colisepticemia and cellulitis in broiler chickens, and salpingitis/peritonitis in commercial layer chickens are the most economically important to the industry (Barnes et al., 2008). This review will focus only on the lessons learned from the numerous attempts to develop a vaccine against the respiratory form of APEC diseases in meat-producing birds.

The economic losses from colibacillosis arise from increased mortality, increased carcass condemnation rates at the time of processing, decreased growth rate and decreased feed conversion efficiency of affected birds. In Brazil, the world's largest exporter of chicken meat, APEC is responsible for 45.2% of condemned poultry carcasses (Fallavena et al., 2000). In addition to the negative economic impact, APEC is also considered a major source for spreading antimicrobial resistance to other bacteria mainly through their plasmids and exchange of other genetic material (Gyles, 2008). This is apparent in Europe, U.S.A. and Australia, where up to 92% of avian *E. coli* isolates were resistant to three or more antimicrobial drugs despite the strict measures on antibiotic use in the poultry industry (Gyles, 2008). Several biological and environmental stresses such as viral or mycoplasma infections, overcrowding and elevated levels of ammonia due to poor ventilation increase the probability of APEC infection (Antao et al., 2008; Dho-Moulin and Fairbrother, 1999). Nevertheless, recent studies report an increase in colibacillosis in the European poultry industry despite advances in biosecurity and strict husbandry measures (Vandekerchove et al., 2005). This suggests that controlling APEC through these indirect measures alone is impractical as *E. coli* is part of the normal microflora of the avian gut and begins to colonize the gut within a few hours of hatching (Dho-Moulin and Fairbrother, 1999) reaching up to 10^6 colony forming units (CFU) per gram of intestinal contents during the first few days of life.

The respiratory form of colibacillosis starts as an airsacculitis that is frequently followed by a generalized infection involving most of the internal organs due to septicemia. The primary route of infection is the respiratory tract, more specifically, the gas-exchange area of the lungs and the air sacs (Pourbakhsh et al., 1997a). The lack of resident macrophages in the birds' air sacs increases their vulnerability to APEC colonization and invasion (Stearns et al., 1987). Therefore, inducing a protective immune response at the respiratory mucosal surface of the bird might contain the infection at an early stage (Zhao et al., 2012). Despite APEC being the most common bacterial pathogen affecting poultry, only a limited number of APEC serogroups; such as O1, O2, and O78, are frequently implicated in field infections (Cloud et al., 1985). Therefore, a vaccine that would provide protection against these three serogroups has the potential to control the majority of APEC outbreaks. APEC possesses several potential virulence factors such as type 1 (F1) and P (Pap or F11) fimbriae (de Pace et al., 2010; Dho-Moulin and Fairbrother, 1999), curli (Ewers et al., 2004), and aerobactin iron-sequestering system (Janben et al., 2001; McPeake et al., 2005). Additional chromosomal regions and ColV plasmids have also been implicated in virulence through genetic analysis (Antao et al., 2008). In particular, the traits associated with serum resistance such as TraT and Iss (for increased serum survival) which are encoded by APEC ColV plasmids are known to play an important role in APEC virulence (Pfaff-McDonough et al., 2000; Rodriguez-Siek et al., 2005).

The type 1 and P fimbriae as well as the aerobactin iron acquisition system are generally conserved across various APEC strains (Ewers et al., 2004; Janben et al., 2001; Rodriguez-Siek et al., 2005). The fimbriae possessed by APEC are known to attach to a variety of host cells and structures. For example, type 1 fimbriae adhere to chicken epithelial cells of the pharynx and trachea. They are composed of several copies of the major subunit, FimA, and a few minor subunits including the FimH adhesin that mediates the attachment of APEC to D-mannose residues present on the host cell (Ashkar et al., 2008; Kisiela et al., 2006). Type 1 fimbriae are expressed by the majority of *E. coli* strains and are widespread among other members of the *Enterobacteriaceae* family (de Pace et al., 2010; Dziva and Stevens, 2008). For instance, Wooley et al. (1992) reported that 100% of APEC strains produced type 1 fimbriae while only 57.5% of nonpathogenic *E. coli* did. Bacterial isolates colonizing the trachea, lungs and air sacs commonly display type I fimbriae, whereas those colonizing deeper tissues or blood do not (Pourbakhsh et al., 1997b). Conversely, the P fimbriae are expressed by bacteria colonizing the deeper tissues such as air sacs, lungs, and internal organs, but not by APEC colonizing the trachea (Pourbakhsh et al., 1997c). The P fimbrial adhesin, PapG forms a specific bond with the glycolipid galabiose (Bjornham et al., 2009). There are 3 allelic variants of PapG (PapGI, PapGII and PapGIII) exist and each allelic variant identifies a different isomer of Gal-α-(1-4)Gal glycolipid present on the host cell with most APEC possessing the