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REVIEW ARTICLE

The development of veterinary vaccines: a review of traditional methods and modern biotechnology approaches

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Abstract The immunization of animals has been carried out for centuries and is generally accepted as the most cost-effective and sustainable method of controlling infectious veterinary diseases. Up to twenty years ago, most veterinary vaccines were either inactivated organisms that were formulated with an oil-based adjuvant or live attenuated vaccines. In many cases, these formulations were not very effective. The discovery of antigen/gene delivery systems has facilitated the development of novel prophylactic and therapeutic veterinary vaccines. To identify vaccine candidates in genomic sequences, a revolutionary approach was established that stems from the assumption that antibodies are more readily able to access surface and secreted than cytoplasm proteins; as such, they represent ideal vaccine candidates. The approach, which is known as reverse vaccinology, uses several bioinformatics algorithms to predict antigen localization and it has been successfully applied to immunize against many veterinary diseases. This review examines some of the main topics that have emerged in the veterinary vaccine field with the use of modern biotechnology techniques.

Introduction

Vaccinations are an effective method of preventing a wide range of animal diseases. The field of vaccinology has yielded several effective vaccines that have significantly reduced the impact of some important diseases in both companion animals and livestock. Today, the vast majority of licensed veterinary vaccines are in the form of live attenuated, killed/inactivated microorganisms, cell membrane compounds or toxoids (McVey & Shi, 2010; Unnikrishnan, Rappuoli, & Serruto, 2012). Live attenuated vaccines can be very effective because they induce both cellular and humoral immune responses (da Costa, Walker, & Bonavia, 2015; Rizzi et al., 2012). However, a major concern that is associated with vaccines of this nature is the potential risk of reversion of the microorganism for a virulent phenotype (Shimoji et al., 2002; Unnikrishnan et al., 2012). Killed/inactivated vaccines are typically safer; however, they may be less effective than attenuated vaccines. The commercial vaccines based on toxoids (inactivated toxins) have some drawbacks since they require complex components in culture medium. The limitations of the three existing vaccine types in combination with the fact that several diseases have yet to be successfully treated with

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an efficient vaccine entails there is a need for better and safer vaccines that can prevent, control or eradicate animal diseases (Dunham, 2002; Redding & Weiner, 2009).

Recombinant vaccines represent an attractive strategy by which the limitations of conventional vaccines can be overcome, and a number of rationally designed and subunit vaccines have already reached the veterinary market. Efforts to develop more effective vaccines against a large number of diseases using recombinant DNA technology are in progress around the world. Recombinant vaccines are developed based on rationally designed recombinant highly purified antigens through structure-based design, epitopes focusing or genomic-based screening (Correia et al., 2014; Dellagostin et al., 2011). In addition to enhancing understanding of the genes responsible for virulence and facilitating the identification of the determinants of protective immune responses, these molecular approaches have provided new methods of developing novel vaccines against infectious, parasitic or metabolic diseases.

However, the inherent immunogenicity of recombinant antigens is often low in comparison to the more traditional vaccines, and there is a need for potent and safe vaccine adjuvants to ensure that recombinant vaccines can succeed. The low immunogenicity frequently observed in recombinant antigens occurs due to a lack of exogenous immune activating components. Recombinant antigens can be offered in different adjuvants, and the immunomodulatory effects are dependent upon the particular adjuvant used in conjunction with specific antigens.

In this review, we summarize the conventional and recombinant vaccines used in veterinary medicine and the molecular approaches that have led to the development of new vaccines in recent years. We have focused on vaccines that target infectious diseases.

Conventional veterinary vaccines

Historically, the development of veterinary vaccines was based on empirical trial-and-error approaches that were designed to mimic, by vaccination, the immunity induced by natural infection (Doolan, Apte, & Proietti, 2014). The conventional ''isolate, inactivate or kill and inject'' approach can induce protection against a wide range of bacterial and viral pathogens. The majority of the licensed veterinary vaccines that are currently in use are inactivated (killed), live-attenuated vaccines or toxoids. In fact, the widespread use of these vaccines has contributed considerably to the improvement of animal and public health. However, conventional vaccines are generally expensive to produce, and need to be administered multiple times to induce optimal immunity (Delany, Rappuoli, & Gregorio, 2014; Meeusen, Walker, Peters, Pastoret, & Jungersen, 2007).

Additionally, the whole-organism approach to vaccination is almost exclusively restricted to pathogens that can be cultured *in vitro*. Although this process has been successful for a number of ''simple'' pathogens with relatively low antigen variability, it has not been effectively applied to vaccinate against pathogens that have high antigenic diversity or/and are capable of evading or misdirecting the host immune response (Doolan et al., 2014). Also, traditional vaccine design is based on a strategy that involves mimicking the immunity induced by natural exposure; however, in the case of many pathogens, this is suboptimal and robust sustained protection may require inducing an immunity that exceeds the natural biological immunity while also ensuring the adverse effects associated with stimulating the inflammatory response are minimized (Zepp, 2010). This is especially true for chronic infections, in which the pathogen is able to co-exist with the host for an indefinite period of time despite the presence of immune responses induced by the host and targeted against the pathogen (Doolan et al., 2014).

Live-attenuated modified vaccines are capable of inducing both humoral and cell-mediated immune responses. In contrast, inactivated vaccines offer improved safety profiles but cannot provide effective long-term protection. They may also cause adverse side effects due to undesirable components. Toxoids induce reliable humoral immunity, but little or no cell-mediated immunity (Moreira et al., 2016). The types and key features of conventional and next-generation approaches to the development of veterinary vaccines are presented in Table 1.

Live-attenuated veterinary vaccines

Live attenuated vaccines are created by passage of viruses or bacteria in an unnatural host or cell. After multiple passages of the virus or bacterial strain in various media, the strain is administered to the natural host in the hope that random mutation has delivered a non-virulent and replicative infectious agent (Meeusen et al., 2007). However, the strains that are present in most of the existing live attenuated bacterial vaccines are not highly protective. In addition, they have many drawbacks. For example, they cause local inflammation and other unwanted reactions and they can revert to virulence. Additional issues include the inability to effectively culture the bacteria or virus, the possibility of inducing an autoimmune response, and the need for refrigerated storage (Babiuk, Pontarollo, Babiuk, Loehr, & Van Drunen Littel-van den Hurk, 2003; Meeusen et al., 2007). As the live attenuated organism can still infect target cells, these vaccines can replicate and induce both cellular and humoral immunity and, generally, do not require an adjuvant to be effective.

The process of producing virus vaccines is very complex because it uses living cells; as such, it is difficult to achieve standardization. Live-attenuated vaccines are also challenging to formulate because of the macromolecular complexity of viruses and bacteria; viruses can be enveloped or non-enveloped. In comparison to inactivated vaccines, live-attenuated viruses are easier to produce, do not require the use of adjuvants in the formulation, and only require minimal downstream processing (van Gelder & Makoschey, 2012). While naturally occurring attenuated viruses or viruses obtained after passage in different animal species or cell cultures were used as vaccine strains in the early vaccines, today, targeted mutagenesis can be applied to generate vaccine virus strains.

The reverse vaccinology approach to vaccine design can create recombinant vaccines that are generally safer and more immunologically defined than the traditional live-attenuated vaccines (Delany et al., 2014). When molecular

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