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Review

Antigen targeting to APC: From mice to veterinary species

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ABSTRACT

Antigen delivery to receptors expressed on antigen presenting cells (APC) has shown to improve immunogenicity of vaccines in mice. An enhancement of cytotoxic T lymphocyte (CTL), helper T cell or humoral responses was obtained depending on the type of APC and the surface molecule targeted. Although this strategy is being also evaluated in livestock animals with promising results, some discrepancies have been found between species and pathogens. The genetic diversity of livestock animals, the different pattern of expression of some receptors among species, the use of different markers to characterize APC in large animals and sometimes the lack of reagents make difficult to compare results obtained in different species. In this review, we summarize the data available regarding antigen targeting to APC receptors in cattle, sheep and pig and discuss the results found in these animals in the context of what has been obtained in mice.

Contents

1. Introduction

Vaccination against pathogens is the most effective way to improve not only human but also animal health. Vaccination of livestock animals mainly relies on the use of classical vaccines which sometimes are not optimal in terms of safety and efficacy. In addition, the use in large animals of new vaccines, based in the inoculation of recombinant proteins, peptides or nucleic acids has shown not to be as effective as in mice, making the development of new approaches that improve their immunogenicity one of the most important areas in animal health research.

Abbreviations: Ab, antibody; APC, antigen presenting cells; ASFv, African swine fever virus; BSA, bovine serum albumin; CLR, c-type lectin receptors; CTL, cytotoxic T lymphocytes; DC, dendritic cells; FMDv, Foot-and-mouth disease virus; GALT, gut associated lymphoid tissue; HA, hemagglutinin; HEL, hen egg lysozyme; hIg, human immunoglobulins; iDC, immature DC; Ig, immunoglobulins; IgSF, immunoglobulin superfamily; MØ, macrophages; mAb, monoclonal antibody; mDC, mature DC; mIg, mouse immunoglobulins; OVA, ovalbumin; PBMC, peripheral blood mononuclear cells; PMN, polymorphonuclear leukocytes; PRR, pattern recognition receptors; scFv, single chain Fv fragments; Siglec, sialic acid binding Ig-like lectins; SLA, swine leukocyte antigens; SLO, secondary lymphoid organs; SRCR, scavenger receptor cystein-rich; TCR, T cell receptor; TLR, toll-like receptors.

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The goal of a vaccine is to induce a memory immune response, a process that initially requires the encounter, in secondary lymphoid organs (SLO), of antigen-loaded APC with naïve lymphocytes. This interaction leads to the expansion of antigen specific B and T lymphocytes that finally would generate specific memory lymphocytes. To this end, different APC types are spread in peripheral tissues to sample antigens that will be processed for their presentation to lymphocytes. APC represent a heterogeneous group of cells with different phenotypes and whose function is not only to uptake, process and present antigen, but also to regulate the magnitude and type of immune response.

Because of their key role in the induction of the immune response, different strategies to improve the efficacy of a vaccine have been focused on APC. Among them, we would emphasize: (1) the use of cytokines or chemokines to recruit APC to the site of antigen inoculation in order to facilitate its uptake (Drake et al., 2000; McKay et al., 2004; Melkebeek et al., 2008; Somasundaram et al., 1999); (2) the coinoculation of antigen with ligands of receptors that trigger signals that induce the expression of MHC and costimulatory molecules on APC to improve antigen presentation (Bonifaz et al., 2004; Jackson et al., 2004; Manoj et al., 2003; Prajeeth et al., 2010); (3) targeting antigen to receptors expressed on the surface of APC, by fusing it to ligands o antibodies (Abs) specific for these receptors, to facilitate antigen uptake, processing or presentation (Caminschi et al., 2009; Tacken et al., 2007; Tacken and Figdor, 2011).

With regard to the latter, a variety of receptors belonging to different families like MHC molecules (Argilaguet et al., 2011; Borrego et al., 2011; Carayanniotis and Barber, 1987; Lunde et al., 2002), Siglec (Backer et al., 2010; Delputte et al., 2011; Poderoso et al., 2011; Revilla et al., 2009; Zhang et al., 2006), TLR (Jackson et al., 2004; Prajeeth et al., 2010), C-type lectin receptors (CLR) (Bonifaz et al., 2004; Lahoud et al., 2009, 2011; Njongmeta et al., 2012), adhesion (Castro et al., 2008; Kurts, 2008) or costimulatory molecules (Boyle et al., 1998; Chaplin et al., 1999; Deliyannis et al., 2000; Shkreta et al., 2003) have been evaluated as candidates for targeting antigen to APC (Tables 1 and 2). Several factors such as the nature of the target receptor, the type of APC and its activation/maturation state or the system used for delivering the vaccine may affect the outcome of the immune response generated (Caminschi et al., 2009; Shortman et al., 2009; Tacken and Figdor, 2011). The target receptor determines the intracellular routing of antigen and therefore its presentation to CD4 or CD8 T cells, or to B cells (Burgdorf et al., 2007; Burgdorf and Kurts, 2008). The interaction of the vector (ligands, Abs or recombinant Ab fragments) with the receptor may also trigger signals in the APC that can affect its activation or maturation state leading either to improve the immune response or to induce tolerance (Caminschi et al., 2009; Shortman et al., 2009; Tacken and Figdor, 2011). Regarding the APC to target, the dogma establishes that dendritic cells (DC) are the most efficient APC stimulating naïve lymphocytes but there is accumulating evidence supporting that other cells, under specific circumstances, can also present antigen to lymphocytes (Bagai et al., 2005; Carrasco and Batista, 2007; Hume, 2008; Junt et al., 2007; Leirião et al., 2012; Moser, 2001; Olazabal et al., 2008; Pozzi et al., 2005; Savinov et al., 2003). Furthermore, antigen targeting to receptors expressed on macrophages, endothelial or M cells has improved immunity both in mice (Backer et al., 2010; Bourges et al., 2007; Kim et al., 2010; Kratzer et al., 2010; Mckenzie et al., 2004; Nochi et al., 2007) and large animals (Delputte et al., 2011; Poderoso et al., 2011), although mechanisms involved in the initiation of the immune response could include the transfer of antigen by these cells to DC located in their proximities (Backer et al., 2010). Different studies also suggest that the location of APC is relevant; thus delivery of the antigen to receptors expressed on APC placed in areas of antigen entry within SLO enhanced the immune response due to the accumulation of antigen in these organs (Corbett et al., 2005), while targeting antigen to cells located in mucosal surfaces induced antigen specific mucosal immunity (Mckenzie et al., 2004).

For its delivery to candidate receptors, antigen can be fused to ligands or Abs, usually mAbs. MAbs show a higher selectivity than ligands, but ligands present some advantages over mAbs as they diminish the risk of side effects, such as immune reactions against them, that may decrease their efficiency, and sometimes they are smaller than mAbs making their tissue penetration easier and faster. However, recombinant technologies allow to design recombinant Ab fragments with similar reactivities to parental Abs but with optimized properties such as a less immunogenic structure or a smaller size (Carter, 2006). These Ab fragments are less immunogenic and show a faster blood clearance and entrance to tissues (Yokota et al., 1992). Furthermore, they can be associated to liposomes, membrane fragments or other delivery systems to increase their effectiveness (Cheng and Allen, 2010; Lu et al., 2011).

The use of recombinant technologies has also allowed the design of DNA vaccines based in the use of plasmids containing antigen-vector sequences. The employment of this strategy that combines DNA vaccination and antigen targeting to APC has shown promising results in the murine model and it is being evaluated to enhance the poor immune responses associated with DNA vaccines in large animals (see Tables 1 and 2).

Although a large number of receptors have been successfully evaluated for antigen targeting in mice, only a few studies using this approach have been reported in livestock animals. Moreover, the lack of reagents and transgenic or knock-out animals has hampered the study of mechanisms involved in the induction of the immune response in animals of veterinary interest. It should be also pointed out that the genetic diversity of livestock animals, their size, the anatomical differences among their immune systems and that of the mouse or the different pattern of expression of some receptors among species make difficult to translate the results obtained in mice to those species. Therefore, there is a need to test each antigen targeting strategy in the species of interest before its application. Here, we will review the work reported on antigen delivery to APC receptors in pig, sheep and cattle and discuss the results in the context of what it has been shown in the murine model.

2. To which cells should the antigen be delivered?

To understand the outcome of antigen delivery to receptors expressed on APC it is necessary to know the biology of these cells. Much of the work reported on antigen targeting to APC receptors in mice has been focused on DC or their subtypes (Caminschi et al., 2009; Tacken et al., 2007; Tacken and Figdor, 2011). In this regard, it is well established the central role of DC in the processing of antigens for presentation and activation of naïve T cells and in the regulation of the resultant immune responses. Mouse DC have been classified based on the expression of CD8α in several subsets that display different abilities to activate naïve lymphocytes (Hashimoto et al., 2011) (Table 3). $CD8\alpha^+$ DC are particularly efficient at cross-presenting antigens on MHC-I molecules, while $CD8\alpha^-$ DC are better for MHC-II antigen presentation. Differences in antigen processing are intrinsic to these DC subsets and are associated with distinct expression of proteins involved in these processes. In this regard, $CD8\alpha^+$ DC are enriched in Tap1, Tap2, calreticulin, calnexin, Sec61, ERp57, ERAAP as well as cystatin B and C which are involved in MHC-I presentation. By contrast, $CD8\alpha^-$ DC express high levels of cathepsins C, H and Z, asparagine endopeptidase, GILT, and H2-Mbeta 1, which participate in the MHC-II antigen processing pathway (Dudziak et al., 2007). In this context,