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International Journal of Vaccines & Vaccination

Review Article

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A message from the immune system: a vaccine technology in needs of exploration!

Abstract

A vaccine technology based on presenting the antigen in the context of its antibody; that is an antigen-antibody complex vaccine has been successfully applied to developing at least two vaccines against two diseases of value to the veterinary field. The technology is based on complexing the antigen with its homologous antibody to form an antigen-antibody complex (AAC) that can then be administered as a preformed AAC. Antigens can be a whole live or killed/attenuated virus/bacterium, fragment of a virus/bacterium, peptide(s), or protein(s)/glycoprotein(s). Polyclonal or monoclonal IgG isotype antibody is the preferred antibody to formulate the AAC with Fab or F(ab')2 being either ineffective or much less effective in generating an immune response comparable to that generated by AAC. Published research has shown quantitative and qualitative gains in the immune handling and response to such AAC vaccines. Lower antigenic mass with less need for adjuvants, directed delivery of antigens, enhanced efficiency of antigen recognition and uptake, processing and presentation to immune cells, recruitment of immune effector cells that otherwise would have not been recruited with conventional antigen alone, earlier and faster immune response, high affinity and quality antibodies similar to that obtained during a secondary immune response, changes in cytokine profiles favoring Th2 profile, and in the case of AAC containing a live virus the ability to control timing and extent of viral replication. The mechanism of action is believed to be through FcRs, possibly through the activating FcRs, requiring Ag: Ab ratio of about molar equivalency, or appropriate neutralization titer (live AAC). Excess antibody, but not Ag was shown to be immunosuppressive, possibly working through inhibitory FcRs. We believe that antigens presented as AAC are "groomed" antigens stimulating the immune system to express its full or "hidden" "talents" to optimize the immune response with the least efforts or cost to the immune system and the body as a whole. It seems like a message from the immune system telling us a way to explore its full talents.

Keywords: vaccines, antigen-antibody complex vaccines, immune responses,antigen presenting cells

Volume 2 Issue 4 - 2016

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Received: March 01, 2016 | **Published:** August 08, 2016

Abbreviations: AAC, antigen-antibody complex; Ab, antibody; Ag, antigen; APC, antigen presenting cells; DC, dendritic cells; FDC, follicular dendritic cells; FcR, fc receptors; GC, germinal centers; IBDV, infectious bursal disease virus; IC, immune complex; IFN-α, interferon-alpha; IFN-γ, interferon-gamma; IL, interleukin; MHC, major histocompatibility complex; RER, rough endoplasmic reticulum

Introduction

There is no disagreement that vaccines are the most efficient way to compact diseases caused by pathogenic microorganisms. Such an efficient way of "restoring physiological normalcy" seems to gain momentum with other fields, namely the fields of oncology, autoimmunity, and allergy. Since the discovery of the first vaccine by Edward Jenner in 1796,[1] a plethora of approaches and technologies employed to develop vaccines, each aspiring to produce an "ideal vaccine," a vaccine that is safe and efficacious regardless of age or immune status of the recipient, produces high-quality innate and adaptive immune responses after a single application, provide a long-lasting immunity, and obviously cost effective.[2–5] Current vaccine technologies are based on either whole organism (live, attenuated, or killed microorganism), microorganism components (peptide, protein, toxoid, & recombinant), or microorganism genetic components (DNA or RNA) technology-based vaccines. Other approaches employ adjuvants or adjuvant-like molecules (molecules attached to the antigen) demonstrated or believed to provide a better opportunity to a better immune response.

A technology in vaccine development based on an exogenously preformed "antigen-antibody complex: AAC" that can then be administered as a vaccine has gained regulatory approval for two such vaccines with applications in the animal health field. Published data clearly demonstrate better vaccine performance in terms of the quality of the immune responses. This review will examine their formulations and the qualities of the immune responses warranting tremendous gains consequent upon further exploration; But first a brief overview of the immune system and the immune response.

Overview of the immune system

A physiologically functional immune system evolved to include many organs, cells, molecules and pathways, all working together to maintain homeostasis within the body when exposed to signals (antigens or pathogens) disturbant to such a homeostasis. Their collective response is called the immune response. The immune response is composed of two very interconnected arms: innate and adaptive immune responses. Innate immune response (innate immunity) is a non-specific, short-lived immunity which includes built-in cellular and molecular mechanisms aimed at quickly preventing infection or eliminating invaders. On the other hand, adaptive immune response (adaptive immunity) is specific and long-lasting aimed at affording life-long immunity against invading pathogens and is

characterized by the cooperation of two subsets of lymphocytes: T and B lymphocytes which are both naïve until stimulated. The trademark of a successful adaptive immune response is the successful recognition and processing of an exogenous (or endogenous) antigen (Ag) by the proper immunocytes and the subsequent presentation of specific components of the processed Ag to the proper immunocytes. Adaptive immune response leads to immunological memory. Immune cells capable of antigen recognition, processing, and presentation are known as antigen presenting cells (APCs). Some of these APCs are classified as professional APCs (capable of presenting Ag in the context of the Major Histocompatibility Complex MHC class I or MHC class II) and include dendritic cells (DC),[6] follicular dendritic cells (FDC) [7], B cells,[8] Macrophages,[9] and eosinophils.[10,11] Non-professional APCs capable of presenting Ag to MHC I-restricted T cells include, among others, neutrophils and resident phagocytic cells such as Langerhans cells of the skin [12] and Kupffer cells of the liver.

The two classes of MHCs differ in which cell expresses them and in the source of antigen they present to T cells. Class I molecules are expressed on all nucleated cells and present antigens originating in the cytosol such as viral proteins, to CD8+ T cytotoxic (Tc) cells, which recognize and kill any cell expressing such proteins. Class II molecules are expressed mainly on APC and present extracellular antigens to CD4+ T helper (Th) cells, which stimulate B cells to differentiate into plasma antibody-secreting cells or memory cells. Cytosolic processing of soluble Ag includes the proteosomic degradation of Ag to constituent amino acids, which are recycled, but some may persist as peptides. It is these peptides that are sampled, assembled with Class I MHC in the ribosomal rough endoplasmic reticulum (RER) and presented on the surface of the APC as peptide associated with class I MHC.[13] Processing of exogenous antigen includes the ribosomal RER synthesis of Class II MHC, internalization of exogenous Ag and the subsequent endolysosomic degradation of the Ag and the association of some of their peptides with Class II MHC, which is then expressed on the surface of APC.[14] Conventionally, exogenous soluble Ag can be internalized by two mechanisms: pseudopods-engolfed phagocytosis or endocytosis (receptor-mediated endocytosis or pinocytosis). Macrophages and DCs employ both mechanisms; other professional or non-professional APC are weak phagocytic cells and rely on endocytosis for internalization of exogenous Ag. Loading of exogenous Ag into Class I MHC and the subsequent presentation to MHC Class I restricted Tc lymphocytes is known as cross-presentation; DCs have been known to be the most efficient in cross-presentation.[15]

Another process where Ag can be recognized by APC is when antigens are introduced as part of a complex composed of the Ag itself bound to a specific antibody (Ab) against the Ag to form an Antibody-Antigen Complex (AAC) or simply a preformed immune complex (IC). We will use the abbreviation "AAC" as opposed to "IC" to make the distinction between exogenously preformed and endogenously formed "and potentially harmful" IC. Unlike the recognition of a free soluble Ag, antigens introduced as part of an AAC are recognized by binding to the Fc receptors (FcRs) expressed on the surface of several immune and non-immune APCs leading to a mechanism of Ag processing that is documented to be different from that for the conventional Ag processing.

Fc receptors (FcRs) are members of the immunoglobulin superfamily composed of membrane-associated glycoproteins that mediate a vast array of functions triggered by immune complexes. There are three main types of FcRs based on which antibody isotype they bind: FcγRs (binds to IgG isotypes), FcαRs (binds to IgA isotype), and FcεRs (bind to IgE isotype). Furthermore, the three types also differ in cells that express them (DCs, macrophages, granulocytes, NK cells, and T & B cells and others) and their signaling properties.[16–19] FcγRs are the most diverse receptors in the body and contains four families: FcγRI (CD64), FcγRIIA, B, C (CD32A, B, C), FcγRIIIA & B (CD16A & B), and FcγRIV (mice with a human equivalent believed to be FcγRIIIA). All FcγRs are activating receptors with the exception of FcγRIIB being inhibitory.[15] Another FcγRs known as neonatal Fc receptors (FcγRn)[20,21] are expressed on many cells, including epithelial and endothelial cells, macrophages, and DC, and function in carrying ingested milk IgG (from the mother) across the infant's intestine, as well as immune complexes binding and internalization (for more on FcγRs,\ see reference.[15])

AAC formulations

As stated earlier, this review focuses on exogenously preformed and introduced AAC, which is different from endogenously formed immune complexes after an immune response and have been known to cause harm. These AAC can be "first order" (AAC comprising a whole live pathogenic (replicating), inactivated, or whole fragments of a virus or a bacterium complexed to a specific IgG subtype monoclonal or polyclonal Ab) or "second order" (AAC comprising a peptide or a protein/glycoprotein complexed to a specific IgG subtype monoclonal or polyclonal Ab). The use of IgM or IgA isotypes has also been reported, though desirable immune responses were observed with IgG isotypes.[22] The ratio of Ag: Ab in the AAC seems to have an effect with desirable results obtained when the ratio is at molar equivalency[23–27] or a slight excess of the Ag or the Ab.[28,29] Formulations containing excess Ab (but not excess Ag) were found to be immunosuppressive.[30] Our own approach to formulating AAC was based on the neutralizing activity of the Ab[31] and was shown to be very effective, especially when the Ag was a live pathogen,[32–34] providing an accurate and precise formulation and allowing a precise timing of viral replication. The first vaccine employing the AAC vaccine technology was licensed for commercial use in 1994.[32,33] The vaccine was formulated using a live infectious bursal disease virus (IBDV) complexed with chicken anti-IBDV polyclonal antibodies to produce the AAC vaccine. The disease is infectious to many avian species with poultry being the most affected. Immature B cells within the bursa of Fabricius (a primary immune organ) are the target cells for the virus rendering the animal immunosuppressed and incapable of responding immunologically to vaccinations or opportunistic pathogens causing substantial economic losses.[35] Whole antibody molecules (not Fab or F(ab')2 fragments) seem to be needed for the successful induction of the immune system.[36,37] A recombinant form of the AAC (or IC) technology has recently been described.[38]

AAC technology application

Augmentation of immune responses to first- or second-order AAC has been reported for various viral and bacterial antigens, including HIV-1 ,[39–43] Hepatitis B surfaces antigen,[44–50] Ebola protein antigens co-expressed with Ab,[51] autoimmune kidney disease,[52–65] *Equine herpesvirus*,[66] chicken infectious bursal disease virus,[32,33,67–69] Chicken Newcastle disease virus,[34,70] Chicken Reovirus,[71] Chicken anemia virus,[72] *Swine parvavirus*,[25,70] formalin-inactivated *Equine encephalomyelitis*,[26] envelope protein of tick-borne Encephalitis virus,[73,74] gram-negative, rod-shaped *coccobacillus Francisella tularensis*,[75] *Mycobacterium tuberculosis*,[27] and the *Streptococcus mutans*.[76,77] So far, and in the animal health, two AAC-based vaccines gained regulatory approval in multiple countries,[32,33,67–69] however, in the human health, one AAC-based vaccine is in clinical trial.[45,47,49]

Citation: Haddad EE. A message from the immune system: a vaccine technology in needs of exploration! *Int J Vaccines Vaccin.* 2016;2(4):91–97.
DOI: 10.15406/ijvv.2016.02.00039

Application of the AAC technology was also demonstrated on human Reovirus (stain TD3 using a mouse experimental model), avian Infectious Bronchitis, and canine Parvovirus complex.[78] Thus, available data suggest that this vaccine development technology is applicable to both human and animal diseases.

Localization of AAC post administration

Although the route of vaccine introduction seems to be a factor with some vaccines or specific vaccine technologies, antigens introduced as AAC vaccines seem to be localized or trapped mainly by the follicular dendritic cells (FDC) of the splenic germinal centers (GC)[67,79–88] and to a lesser degree other professional and non-professional APC.[89,90] An increase in the number of splenic GC was reported after administration of the AAC relative to administering a comparable amount of the antigen alone.[67,91]

Quantitative and qualitative changes in the immune response

We and others have demonstrated that both "quantitative and qualitative changes"[77] in the immune response occurred in response to encountering the Ag as part of an AAC relative to encountering the Ag alone. These changes were reported in several mammalian as well as avian species and included facilitating presentation,[15,28,83,92–96] enhanced antigenicity of a weak antigen,[97] delayed viral replication[32,68,69,72] (in the case of live virus AAC), lower antigenic mass or dose by several folds,[23,90,95,98–101] an earlier immunity,[76,91] changes specific to B cell such as enhanced B cells activation and differentiation,[29, 82] and the selective enhancement of memory B cells in GC[37,102,103] as well as secondary antibody responses.[104]

We had previously shown[32] (and confirmed later by others[65,66,69]) that AAC containing live virus (live AAC) caused delayed replication of the live virus by a period of 6-8days. The delay was directly proportional to the amount of Ab in the AAC. Such delay in viral replication allowed for the early administration of the AAC vaccine at day 18 of embryonic development to developing chick embryos, three days prior to their birth or hatch. Needless to say that same amount of the virus alone is lethal to the embryo when administered at day18 of embryonic development. What is more? the virus is not safe for administration as a vaccine until after day14 of the bird age. The safety of the live AAC was also significantly enhanced where histological changes in the target organ were less than the severe changes observed with the virus alone. The AAC was immunogenic, generating a protective immunity for the life of the birds. Moreover, we have shown that administration of AAC reduced B cell depletion from target organs, increased germinal centers in the spleen, and the localization of AAC to FDC in the spleen as well as the Bursa of Fabricious.[67]

Changes related to T cells activations and proliferations were also observed,[23,89,100] and included the in vivo Th-independent priming of peptide-specific CD8+ Tc cells[83,92,105] by in vitro peptide AAC-activated DC. Enhancements or alterations of lymphokines were also documented among the changes in the adaptive immune response to AAC, as compared to those observed after administration of Ag alone.[44,105–108] Lymphokines reported to have increased in sera of patients after the administration of Hepatitis-B AAC included interleukin (IL)-2, interferon-gamma (IFN-γ), but not IL-4, IL-6, IL-10, or TNF-α.[44,47] Others reported changes in lymphokine profile suggestive of the influence of AAC on the balance of Th1/Th2 responses and the shift of Th1 to Th2.[105,106,108] Th1 effector cells are effector cells active against intracellular Ags and are activated by IL-10 and IL-12 and their effector cytokines IL-2, IL-10, tumor necrosis factor (TNF)-β, and IFN-γ tend to produce cell-mediated immunity and pro-inflammatory responses. Th2 effector cells are active against extracellular Ags and are activated by IL-4 and their effector cytokines include IL-4, 5, 6, 9, 10, and 13 and tend to elicit strong antibody responses. In summary, these changes were realized as a result of enhanced Ag recognition, processing and presentation, and the recruitment of immune cells bearing FcRs that may not be activated or recalled in response to Ag alone.

Potential mechanism of action (MOA) and concluding remarks

Understanding how an antigen encounters and interacts with the proper immunocytes may lead to the development of better vaccines or at least better formulation of vaccines. Needless to say that Ab paratopes are expected to recognize and bind antigenic epitopes (most likely the dominant epitopes) on the surface of the Ag, thus shielding these dominant epitopes transiently. Furthermore, the binding of Ab to the Ag (virus) was shown to induce structural changes in the topography of the virus surface, exposing new antigenic or highly conserved epitopes or determinants.[73,109–111] Whether it is preserving the antigenicity and the immunogenicity of the dominant epitopes or the exposure of conserved epitopes or both (most likely), the result is an Ag groomed for optimal introduction. We believe that the immune system possesses any array of talents that can be fully expressed if antigens are properly presented, leading to a superior immune response with minimal efforts or cost on the part of the immune system itself. There is ample evidence that the efficiency of Ag recognition and uptake (FcR-mediated), processing (FcR-triggered) and presentation in association of MHC I and II are significantly enhanced when Ag is introduced in the context of an Ab (AAC) as compared to introducing Ag alone. Additionally, antigens introduced as AAC may stimulate immune cells that otherwise would have not been stimulated with an Ag not aided by an antibody. Taken together, it may explain the robustness, efficiency, and the high quality of the immune response that has been equated to that obtained with a conventional secondary immune response.[95] Importantly, in work to date, these exogenously preformed AAC stimulated a beneficial and highly protective responses rather than the pathological response which can result from immune complexes generated in vivo, further substantiating our hypothesis illustrated here that groomed Ag may lead to expression of more powerful immune talents.

Data to date showed that AAC vaccines formulated with a live pathogen (virus) complexed to its homologous antibodies clearly presented a way to control viral replication in terms of initiation, quantity, and duration of viral replication; no other vaccines containing live or attenuated pathogen is capable of such control mechanism. Although the exact mechanism is unknown; antibody half-life, antibody neutralizing capabilities, and the time between internalization (through FcR) and processing (storage) may individually or collectively constitute a delay mechanism of viral replication. Nevertheless, the advantages of such a feature are enormous; foremost is the potential to earlier vaccine administration[32–34,67,69,78] where the vaccine can be timed as to when it is processed. In the veterinary field, it is a common practice to hyperimmunize the mother in the hope that the mother would passively pass its immunity to its progenies, thus affording the progenies immediate (but short) protection. Passive immunization is capable not only of neutralizing and eliminating the wild-type pathogens but also any vaccine agents (regardless if it is

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DOI: 10.15406/ijvv.2016.02.00039

live, attenuated, or killed) administered early in life. AAC vaccines containing live virus were shown to overcome such interferences of passive immunity with vaccine virus.

Another potential for introducing Ag in the context of AAC is the possibility to eliminate the need for an adjuvant.[27] Administration of AAC is anticipated to provide a link between the adaptive immune response and the powerful array of innate immunity relative to administering Ag alone.[112] Vaccines for human application could benefit from such features where the use of adjuvants may be redefined since the use of adjuvant with an AAC-based therapeutic vaccine did not show much improvement.[44] Additionally, technologies for commercial production of humanized antibodies are available and the use of therapeutic antibodies is well established. In conclusion, there are strong data showing immune enhancements and advantages of presenting Ag in the form of AAC relative to presenting Ag alone. Is it possible that the immune system prefers antigens delivered by one of its own mailmen?

Acknowledgments

None.

Conflicts of interest

Author declares there are no conflicts of interest.

Funding

None.

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Citation: Haddad EE. A message from the immune system: a vaccine technology in needs of exploration! *Int J Vaccines Vaccin.* 2016;2(4):91–97.
DOI: 10.15406/ijvv.2016.02.00039

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Citation: Haddad EE. A message from the immune system: a vaccine technology in needs of exploration! *Int J Vaccines Vaccin.* 2016;2(4):91–97.
DOI: 10.15406/ijvv.2016.02.00039