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Mucosal Immunology and Vaccination

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REVIEW ARTICLE

Mucosal Immunology and Vaccination

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Abstract:

There is currently great interest in developing mucosal vaccines against a variety of microbial pathogens. Vaccine delivery systems can target respiratory or intestinal mucosal tissue and stimulate immune response and be particularly effective against these infections. In a healthy human adult, mucosal immune system contributes almost 80% of all immunocytes. The administration of mucosal vaccines does not require the use of needles, increasing vaccine compliance, reducing logistical burden, and minimizing the risks of blood transmissible infections. The primary reason for using a mucosal route of vaccination is that most infections affect or start from mucosal surfaces and that in these infections, topical application of a vaccine is often required to induce a protective immune response both innate and adaptive at the site of pathogen entry. Immunoprophylaxis by the mucosal route is an important approach to controlling mucosally acquired infections. The ability to induce a balanced systemic and secretory immune response following immunization is determined by a complex set of interacting factors. These include the nature of the antigens and route of administration, the nature of the mucosal microenvironment, the immunologic vehicles employed for vaccine delivery, and the effects of bystander immunologic and antigen-related events occurring concurrently in the mucosal environment.

Keywords: Mucosal vaccines, vaccine delivery system, route of vaccination.

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Introduction

There is currently great interest in developing mucosal vaccines against a variety of microbial pathogens. In the developing world, infections in the respiratory and intestinal tracts are major causes of sickness and death, especially among children. Vaccine delivery systems can target respiratory or intestinal mucosal tissue and stimulate immune response and be particularly effective against these infections.

Mucosal Immune System

The mucosa-associated lymphoid tissues (MALT) represent a highly compartmentalized immunological system. The primary reason for using a mucosal route of vaccination is that most infections affect or start from mucosal surfaces, and that in these infections, topical application of a vaccine is often required to induce a protective immune response both

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innate and adaptive at the site of pathogen entry [1]. The mucous membranes covering the aerodigestive and the urogenital tract as well as the eye, the inner ear and the ducts of all exocrine glands are endowed

with powerful chemical and mechanical cleansing mechanisms that degrade and repel most foreign matter.

Mucosal vaccines have currently been investigated using a broad spectrum of nanocarrier systems such as multiple emulsions, liposomes, polymeric nanoparticles, dendrimers etc. Although mucosal application of vaccines is attractive for many reasons, only a few mucosal vaccines, mostly oral, have been approved for human use so far. In a healthy human adult, mucosal immune system contributes almost 80% of all immunocytes.

Common Mucosal Immune System (CMIS) [2-4] involving the immunologic network operating on external mucosal surfaces consists of gut-associated lymphoid tissue (GALT), the lymphoid structures associated with bronchoepithelium and lower respiratory tract (BALT), ocular tissue, upper airway, salivary glands, tonsils and nasopharynx (NALT), larynx (LALT), middle ear cavity, male and female genital tracts, mammary glands, and the products of lactation. The organized lymphoid follicles in the GALT and BALT are considered the principal inductive sites of mucosal immune response.

Immunological induction at one mucosal site often results in immune responses at distal mucosal sites and immunization of one mucosal inductive site may induce mucosal immune responses in all mucosal effector tissues. As more extensively reviewed elsewhere antigens taken up by absorptive epithelial cells and specialized epithelial cells (membrane, or M cells) in mucosal inductive sites can be shuttled to, or directly captured by professional antigen-presenting cells (APCs; including dendritic cells (DCs), B lymphocytes and macrophages), and presented to conventional CD4⁺ and CD8⁺ $\alpha\beta$ T cells, all located in the inductive sites. Certain antigens may also be processed and presented directly by epithelial cells to neighbouring intraepithelial T cells, including T cells with limited repertoire diversity. Immune responses in mucosal tissues are governed by the nature of the antigen, the type of APCs involved, and the local microenvironment. The major antibody isotype in external secretions is secretory immunoglobulin A

(SIgA). The major effector cells in the mucosal surfaces are not IgA B cells, but T lymphocytes of CD41 as well as CD81 phenotypes. It is estimated that T lymphocytes may represent up to 80% of the entire mucosal lymphoid cell population

The compartmentalization within the mucosal immune system places constraints on the choice of vaccination route for inducing effective immune responses at the desired sites. Thus, whereas oral immunization may induce substantial antibody responses in the small intestine (strongest in the proximal segment), ascending colon and mammary and salivary glands, it is relatively inefficient at evoking an IgA antibody response in the distal segments of the large intestines, tonsils or female genital tract mucosa [5-7]. Conversely, rectal immunization evokes strong local antibody responses in the rectum but little, if any, response in the small intestine and in the proximal colon [6-8]. Nasal or tonsillar immunization in humans results in antibody responses in the upper airway mucosa and regional secretions (saliva, nasal secretions) without evoking an immune response in the gut [9, 10]; however, and of special interest for possible vaccination against HIV and other sexually transmitted infections, not only vaginal but also nasal immunization has been found to give rise to substantial IgA and IgG antibody responses in the human cervicovaginal mucosae [7-9]. Another notable finding, if it can be confirmed in humans, is that in mice, transcutaneous immunization may induce a mucosal immune response in the female genital tract [10-12]. It should also be borne in mind that the menstrual status of females may influence the intensity of immune responses in genital secretions.

Future Promise

Immunoprophylaxis by the mucosal route is an important approach to controlling mucosally acquired infections. The ability to induce a balanced systemic and secretory immune response following immunization is determined by a complex set of interacting factors. These include the nature of the antigens and route of administration, the nature of the mucosal microenvironment, the immunologic vehicles employed for vaccine delivery, and the effects of bystander immunologic and antigen-related

events occurring concurrently in the mucosal environment. The development of mucosal and systemic immune response or the induction of mucosally induced systemic immunologic hyporesponsiveness (mucosal tolerance) depends on the nature of antigenic simulation of specialized lymphoid structures and the eventual expression of Th1 versus Th2 or Th3 T-cell responses and the expression of proinflammatory versus immunoregulatory cytokines. The mucosal vaccines currently approved for human use include typhoid, cholera, adenovirus, OPV, and rotavirus vaccines. Except OPV none of the presently available vaccines are recommended for routine childhood immunization. Thus, future mucosal vaccine development must involve other strategies. These include development of nonreplicating subunit vaccines, DNA vaccines, plant and other recombinant products, and the use of mucosal adjuvants or more effective vaccine delivery systems to conserve the functional integrity and the antigen mass of vaccines delivered into the relatively harsh mucosal microenvironment.

Current research is providing new insights into the function of mucosal tissues and the interplay of innate and adaptive immune responses which results in immune protection at mucosal surfaces. These advances promise to accelerate the development and testing of new mucosal vaccines against many human diseases including HIV/AIDS [3].

Another promising avenue for mucosal vaccines is the bacterial adhesins. Mucosal antibodies to these proteins block the pathogen's ability to penetrate mucosal barriers. Adhesins are very attractive options because of the highly conserved nature of these proteins due to their association with conserved host receptor proteins. The pilus-associated adhesin FimH from uropathogenic *E. coli* binding to mannose-oligosaccharides is a vaccine target. Mucosally administered vaccines containing FimH are in clinical trials that will assess their efficacy compared with parenterally administered vaccines. Furthermore, the recently approved acellular pertussis vaccine also contains adhesins, i.e., the filamentous hemagglutinin and pertactin, which recognize sulphated sugars on glycoconjugates and

the integrin-binding protein motif Arg-Gly-Asp, respectively. This indicates that adhesin-specific immunity might be a successful approach for generating mucosal protection against pathogen.

Conclusion

The advantages of this new innovative route of vaccination are:

- Induction of an immune response at the site of administration.
- Immunization at one mucosal site can induce specific responses at distant sites, providing protective mucosal immunity.
- Mucosal vaccines induce systemic immunity, including humoral and cell-mediated responses.
- The administration of mucosal vaccines does not require the use of needles, increasing vaccine compliance, reducing logistical burden, and minimizing the risks of blood transmissible infections.

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