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Review

The mucosal immune system for vaccine development

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ABSTRACT

Mucosal surfaces are continuously exposed to the external environment and therefore represent the largest lymphoid organ of the body. In the mucosal immune system, gut-associated lymphoid tissues (GALTs), including Peyer's patches and isolated lymphoid follicles, play an important role in the induction of antigen-specific immune responses in the gut. GALTs have unique organogenesis characteristics and interact with the network of dendritic cells and T cells for the simultaneous induction and regulation of IgA responses and oral tolerance. In these lymphoid tissues, antigens are up taken by M cells in the epithelial layer, and antigen-specific immune responses are subsequently initiated by GALT cells. Nasopharynx- and tear-duct-associated lymphoid tissues (NALTs and TALTs) are key organized lymphoid structures in the respiratory tract and ocular cavities, respectively, and have been shown to interact with each other. Mucosal surfaces are also characterized by host-microbe interactions that affect the genesis and maturation of mucosa-associated lymphoid tissues and the induction and regulation of innate and acquired mucosal immune responses. Because most harmful pathogens enter the body through mucosal surfaces by ingestion, inhalation, or sexual contact, the mucosa is a candidate site for vaccination. Mucosal vaccination has some physiological and practical advantages, such as decreased costs and reduced risk of needle-stick injuries and transmission of bloodborne diseases, and it is painless. Recently, the application of modern bioengineering and biochemical engineering technologies, including gene transformation and manipulation systems, resulted in the development of systems to express vaccine antigens in transgenic plants and nanogels, which will usher in a new era of delivery systems for mucosal vaccine antigens. In this review, based on some of our research group's thirty seven years of progress and effort, we highlight the unique features of mucosal immune systems and the application of mucosal immunity to the development of a new generation of vaccines.

Abbreviations: APC, antigen presenting cell; cCHP, cationic type of cholesteryl group-bearing pullulan; CCL, CC chemokine ligand; CCR, CC chemokine receptor; CMIS, common mucosal immune system; CT, cholera toxin; CTB, cholera enterotoxin B subunit; CXCL, CXC chemokine ligand; CXCR, CXC chemokine receptor; DC, dendritic cell; Ig, immunoglobulin; IgA$^+$ B cell, IgA-committed B cell; FAE, follicle-associated epithelium; GALT, gut-associated lymphoid tissue; GI, gastrointestinal; gp2, glycoprotein 2; Id2, inhibitor of DNA binding 2; IL, Interleukin; ILF, isolated lymphoid follicle; LP, lamina propria; LPS, lipopolysaccharide; LT, heat-labile enterotoxin; LTB, heat-labile enterotoxin B subunit; MALT, mucosa-associated lymphoid tissue; M cell, microfold/membranous cell; NALT, nasopharynx-associated lymphoid tissue; PP, Peyer's patch; PspA, pneumococcal surface protein A; RANKL, receptor activator of nuclear factor κB ligand; RORγt, retinoic-acid-receptor-related orphan receptor-γ; SIgA, secretory immunoglobulin A; TALT, tear duct-associated lymphoid tissue; TGF, transforming growth factor; Th, T helper; TLR, toll-like receptor; TNFR, tumor necrosis factor receptor; Treg, regulatory T; UEA-1, ulex europaeus agglutinin 1.

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1. Introduction

The mucosae of the airways, oral cavities, digestive tracts, ocular cavities, and genitourinary tracts provide the interface for interactions between a host multicellular organism and its external environment. These mucosal sites form one of the largest organs of the body, collectively covering a surface area of more than 400 m^2, and maintain immunological homeostasis through innate and acquired immunity [1]. Due to its continuous exposure to the outside environment and its vast surface area, the mucosal surface is the major route of entry for numerous pathogens [2]. Therefore, to protect against countless invasions at the mucosal surface, the host is equipped with physical and biological barriers. These include epithelial cells joined firmly by tight junction proteins and a dense layer of mucins [3] as well as antimicrobial peptides, such as defensins produced by epithelial cells [4]. In addition, the mucosal tissues are heavily populated with both innate and acquired immune cells, and their surfaces are the location of the secretory immune system, whose major immunoglobulin is secretory immunoglobulin A (SIgA) [5].

Past efforts and recent advances in the field of mucosal immunology have contributed extensively to our understanding of this intricate immune system. In addition, there has been an increasing push to develop vaccines that can be delivered through the mucosal route, because the initiation of immune reactions at mucosal sites can provide both systemic and mucosal protection. In contrast, conventional vaccines injected into the tissues or bloodstream do not usually provide effective mucosal protection [6]. Despite the need, considerable scientific challenges still exist in the development of mucosal vaccines because our understanding of mucosal immunity remains limited.

Here, we highlight the unique features of the mucosal immune system and discuss the application of mucosal immunity to the development of a new generation of vaccines.

2. Unique characteristics of the mucosal immune system in the aerodigestive tract

The mucosal immune system consists of an integrated network of tissues, lymphoid and nonlymphoid cells and effector molecules, including antibodies, chemokines, and cytokines, all of which are responsible for orchestrating innate and adaptive immune responses by responding to invading pathogens during infection and to antigens delivered during vaccination [1]. Moreover, most mucosa-associated tissues and mucosae are home to numerous endogenous microorganisms, most of which harmlessly coexist with the host [7]. The mucosal immune system is thus responsible for mediating the symbiotic relationship between the host and these microorganisms and at the same time functioning as the first line of defense against harmful invading pathogens [2].

The mucosal immune system is functionally and anatomically divided into two main components: the organized mucosa-associated lymphoid tissues (MALTs), where antigen-specific immune responses are initiated, and the diffuse lamina propria (LP) region and glandular tissues, which are effector sites for antibody production and immune cell-mediated responses (Fig. 1) [2,8]. There is constant migration of antigen-primed immune cells from inductive sites to effector sites, and this forms the cellular basis for the common mucosal immune system (CMIS) [2,9]. MALTs, which share many immunological features with secondary lymphoid organs, are characterized by their unique mucosa-associated features. Because they lack an afferent lymphatic system, they have a unique antigen-sampling system, which is represented by the specialized microfold or membranous cells (M cells) that lie within the epithelial layer of the mucosal tissues (e.g., MALT) [10].

MALTs also contain all of the immunocompetent cells, such as dendritic cells (DCs), macrophages, T cells, and B cells, that are required for the generation of an antigen-specific immune response [11]. The first step in a typical immune response is when an ingested antigen is taken up by M cells to be presented to antigen-presenting cells (APCs), such as DCs, which process antigen into peptides and transport the peptides on their MHC class I or II molecules to underlying T-cell zones [12,13]. Chemokine–chemokine receptor interactions (e.g., those between CC chemokine ligand [CCL]19 and CC chemokine receptor [CCR]7 and between CCL20 and CCR6) play an important role in the transport of DCs to the T-cell zones. [14]. In the T-cell zones, peptide antigen is presented to naïve T cells for the generation of antigen-specific T cells, including Th1, Th2, Th17, and cytotoxic T cells. As a consequence of antigen-specific interactions, antigen-primed T cells support IgA class switching and somatic hypermutation of B cells in the germinal centers and B-cell zones [15]. Molecular interactions, such as those of CD40/CD40 ligand, and the action of members of the IgA-associated cytokine family (e.g., transforming growth factor [TGF]-β, interleukin [IL]-2, IL-4, IL-5, IL-6, and IL-10) also play important roles in T-cell help for inducing IgA-producing B cells and their differentiation into plasma cells [16–18] (Fig. 1).

After IgA class switching and affinity maturation, IgA-committed B cells (IgA^+ B cells) migrate from inductive sites, such as Peyer's patches (PPs) and nasopharynx-associated lymphoid tissue (NALT), to the regional lymph nodes through the efferent lymph vessels, and antigen-specific $CD4^+$ T cells and IgA^+ B cells then migrate to the effector sites, such as LP regions [8]. For their migration from the inductive to effector sites, mucosal DCs produce retinoic acids, which induce the expression of α4β7 and CCR9 on both B and T cells and augment the IgA-switching process and migration capacity in PPs, resulting in selective trafficking to the effector sites of the intestinal LP [15]. Under the influence of the mucosal homing and imprinting system, antigen-specific IgA^+ B cells that have migrated undergo final differentiation into plasma cells under the influence of Th2-type cytokines (e.g., IL-5 and IL-6) for the production of the dimeric or polymeric form of IgA [19,20]. A basolateral polymeric Ig receptor expressed by epithelial cells at LP regions binds to and endocytoses polymeric IgA. The endocytosed IgA then is transported via intracellular vesicular compartments to the apical surfaces, where the IgA complex composed of the polymeric IgA and Ig receptor is cleaved to become SIgA and is secreted externally [21] (Fig. 1).

2.1. Gut-associated lymphoid tissue as the 'command center' for mucosal immunity

The primary inductive sites on the gut-associated lymphoid tissues (GALTs), where most of the IgA responses are initiated, include organized follicular structures such as the PPs, cryptopatches, and isolated lymphoid follicles (ILFs) [2]. PPs, the most extensively studied mucosal inductive tissues, are considered to be one of the largest organized lymphoid tissues in the gastrointestinal (GI) immune system [2]. Organogenesis of PPs is initiated during embryogenesis. In embryonic mice, the expression of vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 on stromal cells of the gut, termed PP organizer cells, is the signal that initiates PP formation [22]. This signal is followed immediately by the appearance of PP inducer cells, which are a component of lymphoid tissue inducer cells that have a unique pattern of cell surface markers: $IL\text{-}7R^+CD3^-CD4^+CD45^+$ [22,23] (Fig. 2). PP inducer cells express lymphotoxins α and β, which form a heterotrimer and interact with the lymphotoxin β receptor, a member of the tumor necrosis factor receptor (TNFR) family, on stromal cells to provide the next wave of signals to induce the organization of PPs [22,24]. The importance of these factors in PP organogenesis is demonstrated