Chapter 3
The Mucosal B-Cell System

Per Brandtzaeg and Finn-Eirik Johansen

Abstract The mucosal B-cell system forms the adaptive basis for humoral immune defense of the extensive mucosae. Such antibody protection depends on a complex cooperation between local B cells and secretory epithelia. Mucosa-associated lymphoid tissue (MALT) gives rise to activated B cells with striking J-chain expression that are seeded to local and distant secretory effector sites. Such homing is the biological prerequisite for local plasma cell (PC) production of polymeric immunoglobulin A (pIgA, mainly dimers) and pentameric IgM with high affinity to the epithelial plg receptor that readily can export these antibodies to the mucosal surfaces. The J chain is also produced by IgG- and IgD-producing PCs occurring at secretory tissue sites; these PC isotypes may be considered as ‘spin-offs’ from early effector clones that through class switch are on their way to pIgA production.

Abundant evidence supports the notion that intestinal PCs are largely derived from B cells initially activated in gut-associated lymphoid tissue (GALT). Nevertheless, insufficient knowledge exists concerning the relative importance of M cells, major histocompatibility complex class II-expressing epithelial cells, and professional antigen-presenting cells for the uptake, processing, and presentation of luminal antigens in GALT to accomplish the extensive and sustained priming and expansion of mucosal B cells. Also, it is unclear how the germinal center reaction in GALT so strikingly can promote class switch to IgA and expression of J chain, but the commensal microbiota appears to contribute to both the diversification and memory of MALT responses.

Although B-cell migration from GALT to the intestinal lamina propria is guided by rather well-defined adhesion molecules and chemokines/chemokine receptors, the cues directing preferential homing to different segments of the gut require better definition. This is even more so for the molecules involved in homing of mucosal B cells to secretory effector sites beyond the gut. In this respect, the role of Waldeyer’s

P. Brandtzaeg
Laboratory for Immunohistochemistry and Immunopathology (LIIPAT), Institute and Division of Pathology, University of Oslo, Rikshospitalet University Hospital, N-0027 Oslo, Norway
e-mail: per.brandtzaeg@medisin.uio.no
ring (including the palatine tonsils and adenoids) as a regional MALT in humans needs further characterization, although the balance of evidence suggests that it functions as nasopharynx-associated lymphoid tissue (NALT) identified in rodents. Altogether, data suggest a remarkable compartmentalization of the mucosal immune system that must be taken into account in the development of effective local vaccines to protect specifically the airways, eyes, oral cavity, small and large intestines, and female genital tract.

3.1 Introduction

Mucosal epithelia comprise an extensive and vulnerable physical barrier, which is reinforced by numerous innate defense mechanisms cooperating intimately with adaptive immunity, particularly the generation of secretory immunoglobulin A (SIgA) antibodies. Local formation and export of SIgA constitute the largest humoral immune system of the body, being involved in both the control of commensal bacteria and resistance against pathogens.

Prevention of infectious disease by exploiting the SIgA system is a compelling goal in an effort to improve public health in industrialized and developing societies. The rapid expansion of genome-based biotechnology provides a variety of new avenues for mucosal vaccine development, but it is nevertheless essential to learn more about unique features of the mucosal immune system, and characteristics shared with the systemic immune system. Thus, both mucosal and parenteral vaccination relies on immunological memory, yet our understanding of this fundamental characteristic of adaptive immunity remains incomplete.

Most infections involve the mucosae with regard to initial microbial colonization and entry into the body. In fact, diarrheal disease is ranked by WHO as the second most common lethal infection in children under 5 years of age – accounting for at least 20% of the 10.6 million annual deaths in this age group [1]. Repeated episodes of diarrhea, especially when long-lasting and associated with growth failure, also contribute significantly to malnutrition in developing countries. Rotavirus, diarrheagenic *Escherichia coli*, including enterotoxigenic (ETEC) and enteroaggregative strains, *Shigella* spp. and *Cryptosporidium parvum* are among the worst killers. Cholera is an important cause of diarrhea in the Bengal delta and occasionally causes epidemics with devastating effects even outside of Asia. Despite much intensive research, the development of vaccines against many of these important diarrheal pathogens has yet to be successful, and the same is true for common airway infections [2].

Vaccines applied directly to mucosal surfaces would make immunization procedures easier and better suited for mass administration; in poor countries, the avoidance of horizontal spread of infections with contaminated needles would also be a significant advantage [3]. Mucosal vaccination should, moreover, most efficiently induce immune exclusion [4] – a term coined for non-inflammatory antibody shielding at internal body surfaces – mediated principally by SIgA in co-operation