1. INTRODUCTION

The gastrointestinal system is essentially a long muscular tube, the functional surface of which is a thin, mucus-coated layer approx 1 mm thick, that is joined at both ends with the external integument and, thus, is a contact surface with the external environment (1). The surface area of the adult human intestine is estimated to be approx 300 M² (2). This surface is constantly exposed to antigens, which, proximally, is mostly of dietary origin and, distally, tends to be bacterial products derived from colonic flora. Providing a protective barrier at this external surface is complicated by the need to selectively absorb nutrients. To prevent the colonization and/or invasion of the intestinal mucosa by foreign organisms, the intestine makes use of a number of innate and adaptive defense factors. This chapter provides a broad overview of immune responses in the intestine.

2. INNATE IMMUNITY

A palisade of columnar intestinal epithelial cells (IEC) with interspersed mucus-secreting goblet cells maintains the first line of innate mucosal defense. Mucus sheaths the mucosal epithelium and, together with the glycoproteins of the IEC glycocalyx, forms a size-restrictive permeability barrier against luminal antigens (3). Tight junctions between adjacent IEC serve to prevent intercellular passage of antigens and organisms into the intestinal tissues. Thus, under ideal conditions, the majority of luminal contents that gain access to the intestinal tissues are small nutrient molecules transported transcellularly across the IEC.
The integrity of the IEC barrier in the villi and crypts is maintained by constant proliferation of epithelial stem cells located approx halfway down the villi, the progeny of which migrate either downward into the crypt or upward to the tips of the villi. Progeny cells initially have the ability to differentiate into a number of epithelial cell types, such as absorptive IEC, Paneth cells, and goblet cells, undergoing progressive differentiation during migration. These cell types have specialized functions in protection of the mucosa. For instance, Paneth cells, which are located at the bases of the crypts, produce a number of exocrine antimicrobial factors, such as the anion-binding pore-forming $\alpha$-defensins (cryptins) (4), peptidoglycan hydrolyzing lysozyme (5), and phospholipase A2 (6), that contest microbial colonization of the crypt epithelium. In addition to secreting the mucus barrier (7), goblet cells also produce trefoil proteins (8), factors that enhance IEC migration toward sites of injury and are thus believed to play a role in maintaining the integrity of the epithelial barrier (9).

3. ADAPTIVE IMMUNITY

3.1. Organization and Location of Intestinal Lymphocytes

While passive and active innate factors of the intestinal epithelium provide a basic outermost layer of defense against a broad assortment of environmental antigens and organisms, a diverse array of cells of hematopoietic origin are dispersed throughout the underlying lamina propria, clustered in highly organized secondary lymphoid tissues, and intercalated within the IEC palisade. These bone marrow-derived cells include CD4$^+$ T cells, which support and direct many of the effector functions of other cells, CD8$^+$ T cells, and natural killer (NK) cells, which mediate cytotoxicity against infected, transformed, or physiologically stressed self cells. Other cells involved include B lymphocytes, which produce antigen-specific immunoglobulin (Ig) of primarily the IgA isotype and lesser quantities of IgM and IgG (2), macrophages, dendritic cells, and tissue granulocytes, such as mast cells and eosinophils.

Lymphoid tissues of the intestine are typically categorized into two types: (i) inductive tissues, wherein naïve T and B cells as well as antigen-experienced memory cells are primed by gut luminal antigens and then induced to proliferate; and (ii) effector tissues, the sites to which primed lymphocytes migrate and mediate protective immune function (10). Inductive tissues include the Peyer’s patches (PP), the mesenteric lymph nodes (MLN), the appendix, isolated lymphoid follicles (LF), and potentially such structures as the lymphocyte-filled villi (11). Inductive LF, which are aggregates of B and T cells, interdigitating dendritic cells, and macrophages separated from the luminal contents by specialized follicle-associated epithelium (FAE), are distributed along the length of the intestine from the duodenum to the anorectal junction (11). While usually located in the lamina propria (LP) of the antimesenteric gut wall, human follicles may be distributed randomly around the circumference of the gut. Although generally not macroscopically visible, histological examination reveals that they can be extensive and may be either entirely contained within the LP or may have long extensions under the muscularis mucosa, creating structures previously identified as submucosal lymphoid aggregates (11). Effector tissues include the intestinal LP underlying the villus and crypt absorptive epithelium, and the T lymphocyte-dominated intraepithelial lymphocyte (IEL) compartment (1). Collectively, all these tissues are referred to as the gut-associated lymphoid tissue (GALT).

The largest aggregates of inductive lymphoid tissue in the GALT, the PP are considered the premier priming tissue of intestinal immunity (12). Defined as collections of 5 or more LF, PP are roughly analogous to peripheral lymph nodes. Histologically and functionally, the LF and appendix are very similar to the PP, although some question still remains as to whether the appendix may also serve as a primary B cell organ in the human perinatal gut (13). The quantity