Influence of Nutrition on Mucosal Immunity

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Introduction

Several randomized, prospective studies of critically injured trauma patients demonstrate a significant reduction in pneumonia or intra-abdominal abscess in patients receiving enteral nutrition compared with intravenous (IV) nutrition or no post-operative feeding [1–4]. Since these benefits do not occur in well-nourished patients undergoing elective gastrointestinal surgery or less severely injured trauma victims, the results suggest an immunologic or host defense defect induced by severity of injury or by chronic nutritional depletion. With the majority of nutrition-related infectious complications occurring in the respiratory tract, mechanisms protecting moist mucosal surfaces offer an unexplored area of research potential.

Malnutrition and impaired immunity pose significant challenges to clinical and basic science investigators. While systemic immunity has received extensive attention, there has been no cogent explanation for reduction in respiratory host defenses associated with IV feeding until recently. Earlier work implicated increases in bacterial translocation from the gastrointestinal (GI) tract [5, 6], immunologic depression of neutrophils, macrophages, and other cellular components [7, 8], or a generalized atrophy of the epithelial surface with increases in mucosal permeability [9, 10]. While some loss in villus height occurs, the reduction in cellular proliferation occurs to a lesser extent in man than is seen in animal models [11]. Increases in mucosal permeability to macromolecular proteins or bacterial translocation have been noted in some clinical conditions [12, 13], but a clear association between these observations and extraintestinal infections has been elusive.

Alverdy et al. [14] first described reductions in biliary IgA levels in a rat model of parenteral nutrition [14]. Subsequently, Deitch and colleagues [6] correlated decreases in IgA with bacterial overgrowth of aerobic organisms and increases in bacterial translocation. IgA is a primary epithelial defense against intraluminal bacteria and plays an important role in normal intestinal colonization [15]. IgA is transported by mucosal cells via secretory components after its production by the gut-associated lymphoid tissue (GALT). On the moist mucosal surfaces, IgA blocks adherence of pathogens to the mucosa preventing their attachment and subsequent invasion across the mucosal surface. GALT, the primary immunologic protection of all moist mucosal surfaces, functions to prevent invasive infections but is exquisitely sensitive to the route and type of nutrition in animal models.

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The Integrated GALT Network

GALT comprises approximately 50% of total body immunity, accounting for 70–80% of total immunoglobulin production. It consists of at least four main anatomic units: The Peyer's patches of the small intestine; the mesenteric lymph nodes draining the Peyer's patches; the lamina propria residing beneath moist mucosal surfaces; and intraepithelial lymphocytes. Together, this system provides vigilance and protection against invasion by organisms over the epithelial surfaces.

Peyer's patches contain a specialized population of cells necessary for maintenance of mucosal immunity. The surfaces of the Peyer's patches are covered by specialized M cells which incorporate particles from the lumen. These cells transport foreign antigen to the antigen presenting cells (APCs), such as macrophages and dendritic cells, which sensitize naive T and B cells which migrate through the Peyer's patches via the high endothelial venule. Following sensitization, these T and B cells travel to the mesenteric lymph nodes, proliferate, and are released into the thoracic duct and home to the GALT in the lamina propria via the α-4 β-7 integrin on the lymphocyte and the mucosal addressin cell adhesion molecule (MAdCAM)-1 marker on vascular endothelial cells [16]. The lamina propria consists of plasma cells (which have originated from the B cells), T cells, macrophages, and mast cells. Approximately 70% of the cells within the lamina propria have a CD4+ phenotype while 30% are CD8+. A very small percentage of T cells are CD4+/CD8+ or CD4−/CD8+. T cells produce the cytokines necessary for plasma cell function and IgA production. IgA production depends upon an interaction between T helper cell 1 (Th1) IgA-inhibiting-type cytokines (interferon-γ [IFN-γ] and lymphotoxin [tumor necrosis factor (TNF)-β]) and Th2 IgA-stimulating cytokines (interleukin[IL]-4, IL-5, IL-6, and IL-10) [17]. In mice, the cytokines IL-2, IL-4, IL-5, IL-6 trigger maturation of IgA-expressing cells into IgA-secreting cells. IFN-γ and TNF-β are inhibitory to IgA by direct cell inhibition or through inhibition of the release of Th2 IgA-promoting cytokines.

Intraepithelial lymphocytes have a different characteristic phenotype [18]. Approximately 85% are CD8+/CD4−. A smaller population carries the CD8+/CD4+ phenotype with even fewer double-negative, double-positive, or CD4 single-positive cells. Approximately 50% carry the γ/δ T-cell receptor (TCR) as the binding site, a distinct difference from peripheral cell populations. The functional significance of the γ/δ TCR is unclear, but possibly, this distribution limits the responsiveness of intraepithelial lymphocytes to a small numbers of antigens [19]. While the function of intraepithelial lymphocytes is unclear, there is speculation that they influence mucosal permeability, maintain awareness of intraluminal antigens, and produce cytokines which influence underlying B cell function.

T and B cells released into the vascular tree from the thoracic duct also populate extraintestinal mucosal surfaces such as the mammary gland, the upper respiratory tract and airways, the genitourinary tract, and salivary glands, functioning as a source of IgA production for these surfaces. Considered more globally as the mucosal-associated lymphoid tissue (MALT), these extraintestinal cell populations provide protection against invasion by viral and bacterial pathogens while the mammary glands provide passive immunity to neonates.