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Review

The 2016 ESPEN Arvid Wretlind lecture: The gut in stress☆

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SUMMARY

The gut has a major influence on the course of the human stress response in critical illness for several reasons; the quantity of its immune tissue, the extent of interface with the external environment, the expanse of the microbiome, and its access to the systemic circulation. In critical illness, it is not uncommon to lose mucosal barrier function, which exposes the host to the downside effects of luminal contents and epithelial cell regulation. In that setting, the microbiome is converted to a pathobiome, upregulation of metabolic and immune responses occurs, and homeostatic defense systems are compromised. Awareness of this process mandates that greater attention be given to the interplay between the gut and systemic responses, and that modulation of the gastrointestinal tract be considered in every therapeutic intervention in the critical care setting.

1. Introduction

Intensive care specialists have an important interest and appreciation for the degree to which the gut can modulate outcome in critical illness. A greater understanding of how the gut behaves in both health and disease can lead to truly innovative strategies to manage critical illness. Concepts that relate to the role of the gut in critical illness are not new. Maintenance of gut integrity, preventing increases in permeability, supporting the role of commensal bacteria, and appropriate modulation of immune responses are still important [1–3]. Early concepts of gut-derived sepsis and the gut as the motor of multiple organ failure in critical illness have not been discounted [4].

As is true in most aspects of medicine however, the old is the new "new". Research just in the last half decade has provided an exponential increase in understanding of the role of the intestinal microbiome. While the term microbiota refers to the microbial consortia residing within the intestinal tract (bacteria, viruses, and fungi), the term microbiome is more expansive and describes these organisms together with their genes, their gene products (proteins, metabolites), their community structure, and the particulars of their environment. In critical illness, the commensal microbiome seen in health can shift to a virulent pathobiome [1,5,6]. Evidence suggests that the phenotypic expression of both commensal and pathogenic bacteria can change in response to the environment within the gastrointestinal (GI) tract. Recent studies have elucidated new mechanisms by which gut integrity or loss of barrier function impacts clinical outcome [2,3]. With this better understanding of the underlying pathophysiology, clinicians have begun to appreciate that routine strategies in the intensive care unit (ICU) can be deleterious to outcome. But even more importantly, such enhanced knowledge may lead to the development of new strategies to improve outcome in critical illness through manipulation of the intestinal microbiome and gut barrier defenses.

The environment of the GI tract exists as a balance between two physiologic states. In health, barrier function is intact, commensal bacteria support the normal physiology of the gut through symbiosis, and an overall pattern of systemic homeostasis exists. On the other hand, in critical illness, barrier function can be lost resulting in increased permeability, the number of organisms and their virulent expression can be altered creating dysbiosis, and dysregulated immune responses can generate a pattern of inflammation. For a patient in the intensive care unit, management strategies which seek to restore barrier function, symbiosis, and homeostasis can move the patient toward recovery, while failure to reverse the

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vicious cycle of permeability, dysbiosis, and inflammation can lead to death.

2. Health and homeostasis

The intestinal epithelium is a structure comprised of one cell layer that separates the internal host from a harsh external environment. Incredibly, this single layer of intestinal epithelial cells (IECs) not only functions to absorb macro and micronutrients, but also serves as a barrier against invading pathogens, produces hormones and cytokines, and secretes antimicrobial peptides into the lumen of the GI tract [2]. The IECs are continuously communicating with the gut-associated lymphoid tissue (GALT) and the intraluminal bacteria [2].

The epithelial cells that line the GI tract are comprised of four lineages or subtypes: mature IECs responsible for absorption and digestion, goblet cells which secrete mucus, enteroendocrine cells which provide hormonal regulation of digestion, and paneth cells which secrete antimicrobial peptides into the lumen of the GI tract [2,3,7] (See Fig. 1). All four subtypes are derived from a progenitor stem cell located at the junction of the crypts and the villi. As the stem cells proliferate into the mature subtypes, the IEC's, goblet cells, and enteroendocrine cells migrate up the villi from crypt to apex, while the paneth cells move down into the crypts. The cells of the crypts and villi are replaced in their entirety every 3–5 days by this process [8]. Apoptosis is part of this orderly process, and is a strategy by which there is disposal of injured and senescent cells in a non-inflammatory manner. The turnover of epithelial cells by this pattern of programmed cell death is nearly constant. The orderly proliferation, maturation, and migration of the epithelial cells, the regulated apoptosis, and the subsequent replacement by new cells is critical for the maintenance of barrier function and protection from injury [8].

The IECs together with the dendritic cells are in constant communication with the commensal microbiota [9,10] (See Fig. 2). This crosstalk signaling between the host cells and the commensal bacteria is critical for maintaining barrier function and modulating homeostatic immune responses. Communication between the host and the microbiome is facilitated by Pattern Recognition Receptors (PRRs) on the cell surface and in the cytoplasm of the IEC and Microbial-Associated Molecular Patterns (MAMPs) on the surface of the bacterial cell wall [9,10]. PRRs include a family of toll-like receptors (TLRs), types 1–10, on the surface of the epithelial cells, and nod-like receptors (NLRs), types 1 and 2, in the cytoplasm of these cells. The MAMPs on the surface of the bacteria are variable, comprised of peptidoglycans and teichoic acid on gram positive organisms, and lipopolysaccharide, flagellins, and cell wall polysaccharides on gram-negative organisms [9] (See Fig. 3). The PRR-

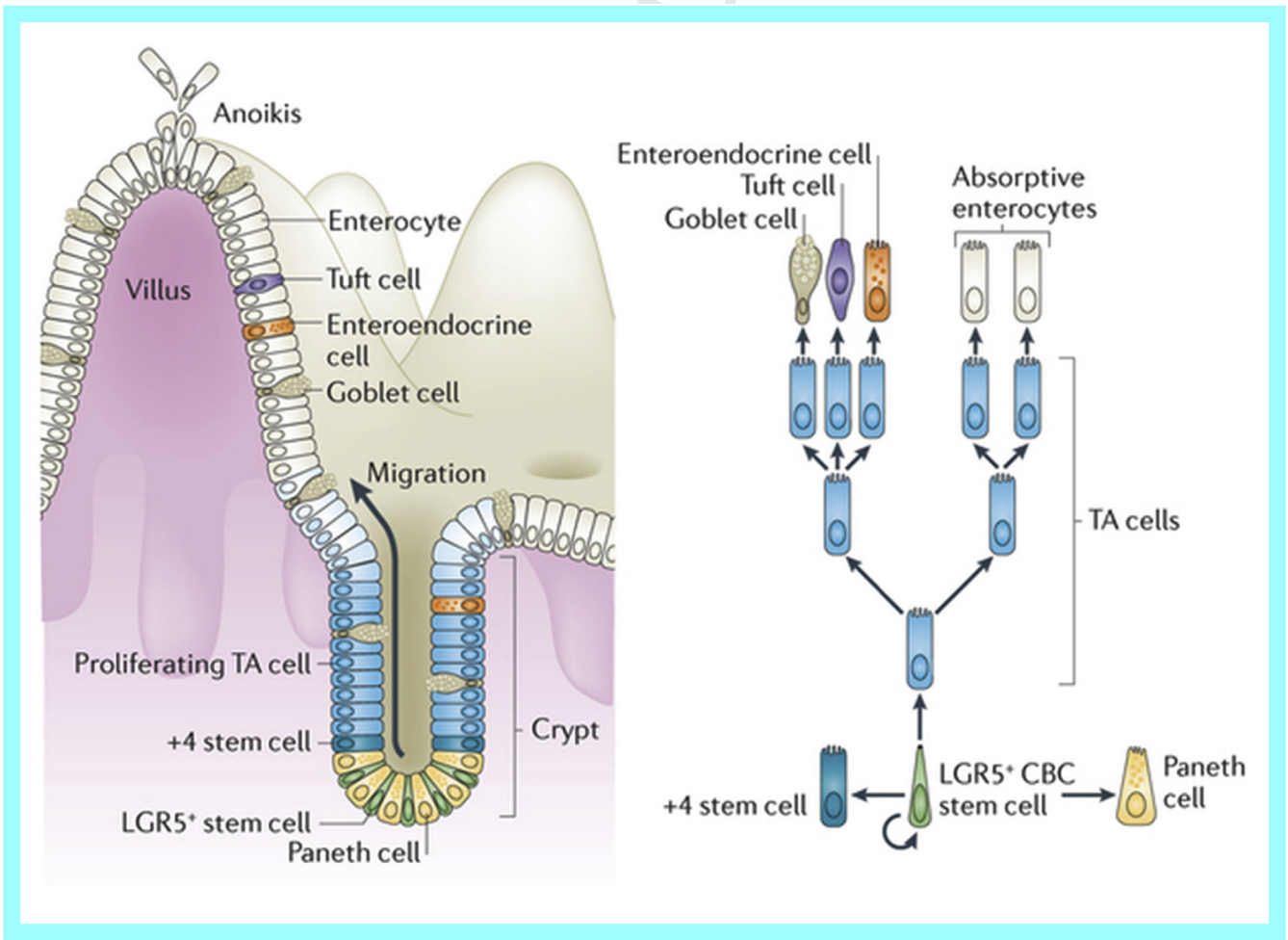

Fig. 1. Structural organization and pattern of self-renewal of the intestinal epithelium [7]. Stem cells are formed in the area of the junction of the crypts and the villi. As they mature into one of four cell types within the intestinal epithelium, the Intestinal Epithelial Cells, Goblet cells, and Enteroendocrine cells migrate up over the villi, while Paneth cells migrate down into the crypts. **Legend**: TA = Transit amplifying cells; LGR5 = Leu-rich repeat-containing G protein-coupled receptor 5-expressing; Anoikis = apoptosis.

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