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Inflammatory signals that regulate intestinal epithelial renewal, differentiation, migration and cell death: Implications for necrotizing enterocolitis

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Abstract

Necrotizing enterocolitis is a disease entity with multiple proposed pathways of pathogenesis. Various combinations of these risk factors, perhaps based on genetic predisposition, possibly lead to the mucosal and epithelial injury that is the hallmark of NEC. Intestinal epithelial integrity is controlled by a tightly regulated balance between proliferation and differentiation of epithelium from intestinal epithelial stem cells and cellular loss by apoptosis. various signaling pathways play a key role in creating and maintaining this balance. The aim of this review article is to outline intestinal epithelial barrier development and structure and the impact of these inflammatory signaling and regulatory pathways as they pertain to the pathogenesis of NEC.

Keywords: Necrotizing enterocolitis; NEC; Signaling; Inflammation; Paneth cells; Stem cells; Crypts; Differentiation; Mucin; Trefoil; Secretory IgA

1. Introduction

Necrotizing enterocolitis (NEC) is an emergency affecting the bowel in neonates, most often in very low birth weight (VLBW) premature newborns. The incidence of NEC in VLBW infants approaches and sometimes exceeds 10% in neonatal intensive care units around the world [1]. This incidence has not changed significantly in the past two decades. However, with improved survival of extremely premature newborns over the past few decades, the prevalence of NEC and its complications have increased [2]. NEC can be often managed medically, but 20–40% of infants need surgical management [3]. Infants that require surgical intervention are at higher risk of mortality and longer-term morbidity including complications such as stoma prolapse or stricture, short bowel syndrome, and impaired long-term growth and neurodevelopmental outcomes [4,5].

Despite a high volume of research in clinical as well as laboratory settings, we still possess only a limited understanding of the pathophysiological mechanisms of this devastating illness. Multiple etiologic factors including immaturity of the preterm newborn intestinal tract, formula feeding, infections, and ischemia have been associated with NEC. A combination of these risk factors, perhaps based on genetic predisposition, possibly lead to the mucosal and epithelial injury that is the initiating event of NEC. Intestinal epithelial integrity depends on a fine balance between proliferation and differentiation of epithelium from intestinal stem cells (ISC) that line the intestinal crypts and cellular loss by apoptosis near the villi tips. Signaling mediated by a variety of pathways plays a key role in creating and maintaining this balance and also in creating a mucosal barrier that serves to reinforce intestinal epithelial integrity. The aim of this article is to provide an in-depth review of intestinal epithelial barrier development and structure, and how they are affected by inflammatory signaling and regulatory pathways, leading to NEC.

2. Development of the intestinal barrier

2.1. Early embryonic development

Containment of absorption from the environment in a closed tube was a key evolutionary step in the development of multicellular organisms. The formation of a specialized

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digestive organ allowed the development of other cells into additional specialized organ systems. This is unlike primitive organisms, which cannot regulate their absorptive surface. Similar to most epithelial surfaces in vertebrates, the epithelium of the small intestine is derived from the endoderm. Exposure to the TGF-β related growth factor, Nodal and Sox-2 allows endodermal cells to express Hhex thereby becoming committed to the anterior endoderm. Conversely, CDX-2 expression in the posterior endoderm leads to upregulation of transcriptional factors that are required for intestinal development, resulting in the development of small and large intestines [6,7]. After successive transformations through pseudostratified squamous epithelium and stratified epithelium to the more mature columnar epithelium, cells begin to undergo differentiation accompanied by villus and secondary lumen formation. Combined with mesenchymal condensation and proliferation this process leads to the development of the crypt-villus units, as the basic building blocks of the small intestinal epithelium. In the large intestine, villi are absent and mature colonocytes form the colonic surface epithelium instead. Significant mesenchymal–endodermal interactions occur throughout the process of intestinal development. Endodermal derived PDGF and Hedgehog signals (mediated by the FoxL1 transcription factor) induce mesenchymal growth into nascent villi, and in turn, mesenchyme-derived signaling pathways such as Wnt/β-catenin-Tcf3 and BMP initiate development and differentiation of the epithelial cells [8,9]. Scattered islands of proliferating cells become more organized in inter-villus spaces, and provide niches populated by precursor stem cells to form the intestinal crypts of Lieberkuhn. Wnt and BMP signaling pathways also play important roles in crypt development – inhibition of these pathways leads to disordered and abnormal crypt formation.

2.2. Cellular differentiation

In the small intestine, crypt base columnar (CBC) stem cells produce progenitor cells that develop into epithelial cells of various types. Initial formation of villi is associated with the first visible signs of epithelial differentiation into absorptive enterocytes, and secretory goblet and enterochromaffin cell types. Crypt development leads to the emergence of another distinctive intestinal secretory epithelial cell type called the Paneth cells, which plays a central role in various functions of the GI tract. Numerous signaling pathways and transcription factors have been identified to be involved in the intricate mechanisms that underlie intestinal epithelial cell differentiation.

Following a cycle of self-renewing asymmetrical division and one or more subsequent transit amplification steps in the crypt stem cell niche, newly formed intestinal epithelial cells differentiate into at least seven different cell types. Of these seven, five are relatively well characterized and two remain to be relatively obscure. The five relatively well characterized members are enterocytes, goblet cells, Paneth cells, enteroendocrine cells and M cells, whereas the more obscure members are the cup cells and tuft cells. As shown in Fig. 1, CBC cells produce progenitor cells that are variably induced by atonal homologue-1 (Atoh1) or hairy enhances of split-1 (Hes1) to differentiate into the various secretory cell types or into absorptive enterocytes respectively [10,11]. Both Atoh-1 and Hes-1 repress and regulate each other. Atoh1 allows

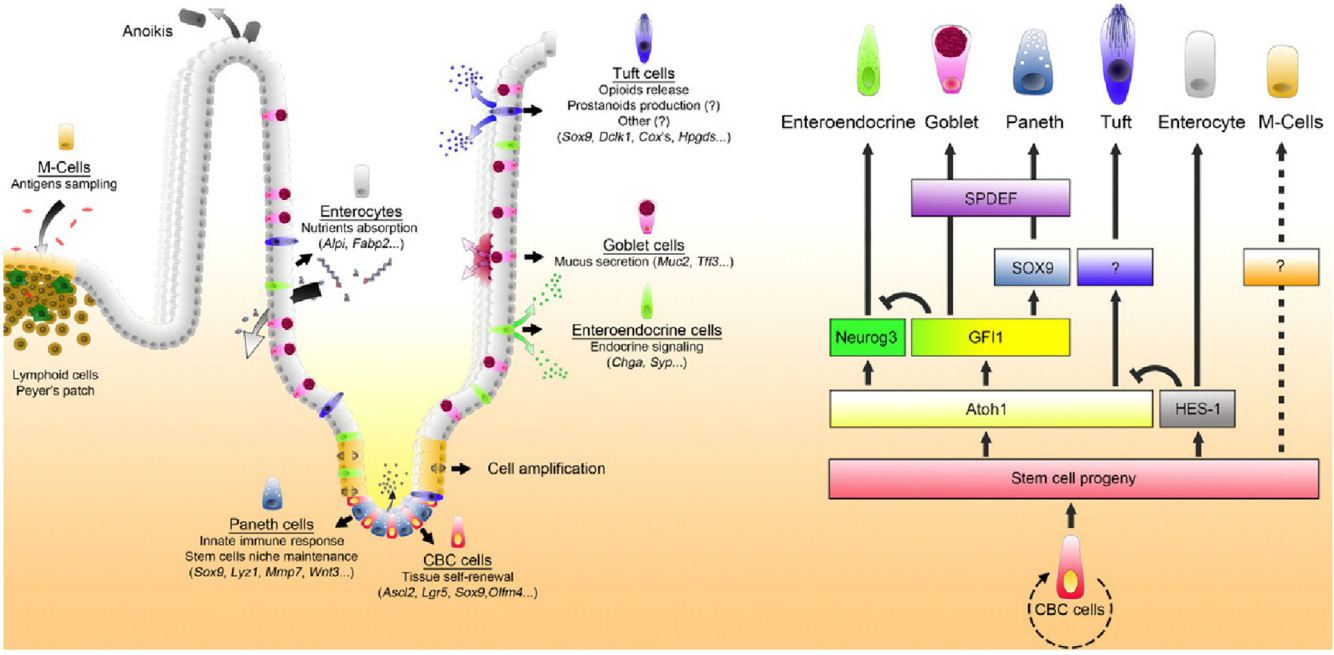

Fig. 1. Schematic of intestinal epithelial differentiation. Adapted from Gerbe et al. [46]. Following the generation of new cells, intestinal epithelial cells must undergo differentiation, which occurs simultaneously with their migration out of the stem cell niche. Transcription factors that drive this differentiation as well as functions of the terminally differentiated, specialized epithelial cells are shown.