Regulation of Paneth Cell Function

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Paneth cells are specialized intestinal epithelial cells that are located at the base of small intestinal crypts and play a vital role in preserving the gut epithelium homeostasis. Paneth cells act as a safeguard from bacterial translocation across the epithelium and constitute the niche for intestinal stem cells in the small intestine by providing multiple niche signals.

Paneth cells RNA-binding proteins noncoding RNAs microRNAs

1. Introduction

The epithelium of mammalian intestine self-renews rapidly and its surfaces are exposed to a wide variety of luminal noxious substances and are colonized by complex microbiota. Most bacteria perform beneficial functions, but they can also alter the intestinal epithelium homeostasis and threaten host health upon tissue invasion [1][2]. The protective intestinal mucosal barrier against luminal toxins, antigens, and bacterial invasion is a complex process consisting of multiple elements, including mucus layer, epithelial layer, and immune defense systems [1][3]. Residing at the bottom of the small intestinal crypts, Paneth cells are highly specialized secretory cells that are critical for maintaining integrity of the small intestinal epithelium by sustaining host defense against enteric pathogens [4][5] and preserving the health of intestinal stem cell niches [6][7]. Paneth cells synthesize an ample number of antibacterial proteins or peptides, including lysozymes, α-defensins, C-type lectins, phospholipase A2, RegIII, MMP-7, CRIP, and xanthine oxidase [5][8][9]. These secretory substances within Paneth cells are initially assembled together and packaged into dense core granules by an endoplasmic reticulum (ER) and Golgi complex network and can be rapidly released from the apical side of the cell into the lumen to protect the epithelium from bacteria, fungi, protozoans, and virus infections [5][6][10]. Paneth cells also provide multiple secreted (Wnts, EGF) and surfaced-bound (Notch ligand) niche signals essential for intestinal stem cell (ISC) maintenance and function in response to pathophysiologic stress [11][12]. Nonetheless, defects in Paneth cells occur commonly in different gut mucosal diseases and compromise the epithelial protection and constant renewal [11][13][14].

Posttranscriptional controls, especially altered mRNA stability and translation by RNA-binding proteins (RBPs) and noncoding RNAs (ncRNAs), are major mechanistic events by which mammalian cells regulate gene expression [15]. After mRNAs are transcribed from DNAs, they are subject to several processing and regulatory steps. Among these processes, alterations in mRNA turnover and translation are mainly governed by the association of specific mRNA sequences (*cis*-elements) with two important types of trans-acting factors such as RBPs and ncRNAs [16][17]. RBPs directly interact with target mRNAs via AU-rich elements (AREs), or GU-rich elements (GREs) distributed in the 3′-untranslated regions (UTRs) and/or coding regions (CRs), and these associations alter mRNA

turnover and translational efficiency positively or negatively [18]. On the other hand, ncRNAs, including microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs) are intimately involved in every level of gene regulation such as transcriptional and posttranscriptional processes, chromatin remodeling, and protein metabolism [16][19][20]. Increasing evidence indicates that RBPs and ncRNAs are a novel class of master posttranscriptional modulators of gut epithelial homeostasis and that disrupted regulation of RBPs such as HuR and ncRNAs including lncRNA *H19* results in Paneth cell defects.

2. Paneth Cells in the Intestinal Epithelium Homeostasis

Paneth cells were first identified in 1888 by Josef Paneth as columnar gut epithelial cells possessing prominent eosinophilic granules in their cytoplasm [13]. Development of Paneth cells is evident in both small intestine and colon at an early gestational age, but they move down to the crypts of the small intestine and disappear in colonic mucosa after birth. Unlike most intestinal epithelial cells (IECs) that are quickly turned over within a few days, Paneth cells can persist for months in healthy individuals. Paneth cells are interspersed between ISCs and constitute Paneth cell/ISC niche essential for continuous mucosal growth [14]. In some pathological conditions such as chronic inflammation, however, Paneth cells abnormally arise in other organs including the esophagus and colon (termed as metaplastic Paneth cells), although the role of metaplastic Paneth cells remains to be elucidated [21]. As summarized in **Table 1**, emerging evidence shows that Paneth cells are crucial for sustaining homeostasis of the intestinal epithelium by enhancing the host defense and promoting constant epithelial renewal. Paneth cell dysfunction exhibits significant detrimental consequences, including diminished clearance of bacterial pathogens, impairment of ISC function, and development of mucosal inflammation [22][21][23].

Table 1. Role of Paneth cells in the intestinal epithelium homeostasis and diseases.

Function	Mechanisms	References
Host defense	AMPs: Lysozyme α-defensin C-type lectins Phospholipase A2 Reg-III MMP-7 CRIP Xanthine oxidase Autophagy Apoptosis	Bel et al. [24]; Xiao et al. [25] Ayabe et at. [23]; Salzman et al. [26]; Porter et al. [27] Riba et al. [5] Boya et al. [8] Bel et al. [24] Peterson et al. [28] Yang et al. [29] Lueschow et al. [13] Clevers et al. [11] Bel et al. [24]; Dikic et al. [30]; Li et al. [31] Gunther et al. [32]; Giammanco et al. [33]
Mucosal renewal	Stem cell niches Niche signaling (Wnt, Notch)	Beumer et al. [6]; Clevers et al. [11] Sato et al. [12]
Impact on diseases	IBD Bacterial Infection Sepsis	Yang et al. [29]; Geng et al. [34] Xiao et al. [35] Riba et al. [5]; Beumer et al. [36]; Salzman et al. [26] Yu et al. [37]

Function	Mechanisms	References
	Cancers	Chatterji et al. [38]; Giammanco et al. [33]
	NEC	Torow et al. [2]; Gunther et al. [32]

2.1. Paneth Cells Enhance Epithelial Defense by Secreting Antimicrobial Peptides/Proteins

As specialized and secretory IECs in the small intestinal mucosa, Paneth cells produce a variety of antimicrobial peptides and proteins [23][28]. Because the surfaces of the small intestinal mucosa are constantly awash with bacteria and their products, Paneth cells continuously synthesize and release antimicrobials at a baseline rate via granule secretion mechanism, with increased amounts secreted on maximum stimulation. In response to bacterial infection, for example, these antimicrobial-rich granules in Paneth cells are released into the crypt lumen, where increased accumulations of antimicrobials prevent bacterial invasion of the crypt and protect the epithelium against infections by enteric pathogens [36][39]. Many antimicrobial proteins/peptides destroy their target bacteria by impairing integrity of the membrane, but some peptides/proteins specifically repress bacterial cell wall synthesis through the association with lipid II [40]. Defensins are a major family of antimicrobial peptides in mammals, and Paneth cells produce many antimicrobial peptides and proteins that are evolutionally related to α-defensins. The α-defensins are only expressed in Paneth cells in mice and contributes to the enteric innate immunity [23][24]. Availability of enteric α-defensins and its impact on epithelial defense are markedly linked to Paneth cell function and homeostasis. Mice overexpressing the *Defa5/6* gene exhibit Paneth cell dysfunction, along with a significant alteration in the composition of resident ileal microbiota, similar to those observed in IBD patients [26]. As altered microflora in human is implicated in pathogenesis of IBD, the quantity and the repertoire of Paneth cell α-defensins and other-related genetic products in such condition alter gut mucosal defense and affect the epithelial integrity by constituting a healthy microbiota or by increasing risk to inflammation and infections in genetically predisposed individuals [26][27][36][39].

Several studies have demonstrated the necessity of autophagy in Paneth cells, including formation of secretory granules, secretion of antimicrobial peptides and/or proteins, and control of host immunity [10][11][13][24][25]. As a conserved intracellular pathway, autophagy sequesters the cytoplasmic structures and pathogens involved in the process of degradation [30][41]. Autophagy is required for maintaining normal structure and function of various cellular organelles such as ER and mitochondria in Paneth cells, while lysozyme secretion by Paneth cells is mediated via secretory autophagy to limit intestinal bacterial infection [24][30]. Mutation of the autophagy-related genes (*Atgs*) leads to dysfunctional mitochondria and ER and subsequent defects in Paneth cells, thus enhancing the release of inflammatory cytokines in dextran sulfate sodium-induced colitis in mice and other pathological conditions [30][31][36][39][42]. Mice with hypomorphic IBD-associated allele *Atg16L1* exhibit reduced Paneth cells, which is associated with an inhibition of secretory granule formation, a decrease in lysozyme synthesis, and an increase in inflammatory cytokines by macrophages [31][32]. The *Atg16L1* deletion in mice causes abnormal alterations such as Paneth cell number, organoid assembly, granule structure, and secretion of antimicrobial peptides [4][27][31]. Loss of *Atg4B*, *Atg5*, or *Atg7* genes also results in Paneth cell defects; all these findings suggest that autophagy plays a critical role in the control of Paneth cell function [43][31].

2.2. Paneth Cells Regulate Intestinal Mucosal Growth by Interacting with Intestinal Stem Cells

The human small intestinal epithelium undergoes ~10^{11} mitoses/day and this rapid and dynamic turnover rate is driven by ISCs, which are tightly regulated by multiple factors at different levels [16][32]. ISCs divide daily and produce bipotent progenitors amplifying and differentiating into absorptive or secretory lineages [12][32]. Paneth cells create the niche for ISCs in the crypts and provide many secreted as well as surfaced-bound niche signals [11][12]. The Paneth cell niche is the microenvironment in which ISCs both reside and receive stimulations that determine their fate in vivo. Emerging evidence indicates that interactions between Paneth cells and ISCs in the intestinal crypts are essential for continuous and rapid intestinal epithelial renewal under various pathophysiological conditions [25][44]. Coculturing of sorted Paneth cells with ISCs dramatically enhances intestinal organoid formation and growth [12], whereas Paneth cell defects results in ISC dysfunction and leads to an inhibition of intestinal mucosal growth [12][25]. In the case of Paneth cell ablation, enteroendocrine and Tuft cells and intestinal stromal cells can also support ISC function [11][45][46].

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