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Review Article

Diverse roles of LPA signaling in the intestinal epithelium

C. Chris Yun[a,b,c,*], *Ajay Kumar*[a]

[a]*Division of Digestive Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA*
[b]*Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA, USA*
[c]*Atlanta VA Medical Center, Decatur, GA, USA*

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ABSTRACT

Lysophosphatidic acid (LPA) is a lipid mediator that modulates a wide variety of cellular functions. Elevated LPA signaling has been reported in patients with colorectal cancer or inflammatory bowel diseases, and the tumorigenic role of LPA has been demonstrated in experimental models of colon cancer. However, emerging evidence indicates the importance of LPA signaling in epithelial wound healing and regulation of intestinal electrolyte transport. Here, we briefly review current knowledge of the biological roles of LPA signaling in the intestinal tract.

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Abbreviations: LPA, lysophosphatidic acid; IEC, intestinal epithelial cell; IBD, inflammatory bowel disease; CRC, colorectal cancer; PA, phosphatidic acid; PLA, phospholipase A; ATX, autotaxin; YAMC, young adult mouse colonic epithelium; MSIE, mouse small intestinal epithelium; HIF-1, hypoxia-inducible factor 1; KLF5, Krüppel-like factor 5; MIF, macrophage migration inhibitory factor; MAGI-3, membrane-associated guanylate kinase with inverted orientation-3; NHERF, Na^+/H^+ exchanger regulatory factor; RhoGEF, Rho guanine nucleotide exchange factor; PLC-β, phospholipase C-β; DSS, dextran sodium sulfate; FAK, focal adhesion kinase; MMP, matrix metalloprotease; COX-2, cyclooxygenase-2; NHE3, Na^+/H^+ exchanger 3; CFTR, cystic fibrosis transmembrane conductance regulator.

*Correspondence to: Division of Digestive Diseases, Department of Medicine, Emory University School of Medicine, Whitehead Research Building, Room 201, 615 Michael Street, Atlanta, GA 30322, USA.
E-mail address: ccyun@emory.edu (C.C. Yun).

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Introduction

The surface of the intestinal tract is lined with a layer of simple columnar epithelial cells. The surface of the small intestine is structurally divided into villus and crypt. The villus increases the surface area for absorption that is carried out by fully differentiated enterocytes. The crypt harbors stem cells and progenitors cells that regenerate the entire population of the intestinal epithelium every three to five days. In addition to carrying out digestion of food and absorption of nutrients, intestinal epithelial cells (IECs) form the first line of defense by separating the body from the lumen of the gut. The hostile luminal microenvironment damages the epithelial barrier that compromises the mucosal innate immunity that can lead to the pathologic conditions, such as inflammatory bowel diseases (IBD), infectious enterocolitis, and colorectal cancer (CRC) [1].

The integrity of intestinal epithelial cells is modulated by several factors that present within the intestinal lumen or the underling submucosa. These include growth factors (transforming growth factor-β, epidermal growth factor, platelet-derived growth factor, and vascular endothelial growth factor), regulatory peptides (trefoil and glucagon-like peptide-2), and non-peptide regulators (polyamine, adenine nucleotide, and glutamine) [1]. Damage to the intestinal surface and the breakdown of cell membrane lipid complexes lead to generation of eicosanoids, such as prostaglandins, thromoboxane, and leukotrienes, which are closely linked to pro-inflammatory responses, bacterial translocation, vasoconstriction, and cell survival [2]. LPA is a pleiotropic lipid molecule with potent effects on cell growth, motility, and inflammatory responses. Studies links LPA to inflammation and cancer, but emerging evidence indicates the roles of LPA in regulation of physiological functions in the gut.

LPA receptor expression in the intestine

During cell injuries and inflammation, LPA is produced by the activated platelets, fibroblasts and even by the injured epithelial cells. The majority of extracellular LPA is thought to be generated by at least two pathways. First involves hydrolysis of the fatty acid moiety from the membrane derived phosphatidic acid (PA) by phospholipase A_1 (PLA_1) and phospholipase A_2 (PLA_2). Another pathway requires the removal of choline moiety from lysophosphatidylcholine (LPC) by lysophospholipase D known as autotaxin (ATX) [3]. In addition to the cellular generation, LPA is present in significant amounts in several types of foodstuffs, including egg, soybean, and cabbage leaves [4]. Interestingly, egg yolk predominantly contains saturated LPA, whereas unsaturated LPA is the dominant LPA species in egg white [4]. Although the amounts of LPA in most of foodstuffs are not known, a recent study has shown the presence of PA in vegetables, such as cabbage leaves and Japanese radish leaves [5]. In an earlier study, the same group has shown that LPA is formed during mastication in the mouth by conversion of PA to LPA by PLA_2 [6]. Because the gastrointestinal tract is the primary site of digestion, biological effects of food-borne LPA carry a great significance. It was shown that unsaturated fat-rich Western diet elevates unsaturated LPA levels without altering saturated LPA in the small intestine of mouse that lacks low density lipid receptor [7]. This study potentially links Western diet to systemic inflammation and dyslipidemia via increased levels of unsaturated LPA.

LPA mediates its effects through a family of G protein-coupled receptors, LPA_{1-6} [8]. Multiple LPA receptors are expressed in the intestinal tract. The most abundant LPA receptors in mouse ileal and colonic epithelial cells are LPA_1 and LPA_5 based on quantitative RT-PCR [9]. The expression levels of LPA_2, LPA_3, and LPA_4 are relatively low in mouse IECs. Similarly, normal intestinal epithelial cell lines such as rat IEC-6, young adult mouse colonic epithelium (YAMC), and mouse small intestinal epithelium (MSIE) cells express LPA_1 at the highest level although expression of other LPA receptors varies depending on the cell lines [10]. Many of the colon cancer cell lines express elevated levels of LPA_2, a trend often observed in other cancer cells [11]. LPA_5 mRNA expression is abundant in freshly isolated IECs from mouse, but most of the cultured epithelial cells of intestine origin, including YAMC, MSIE, Caco-2, and HCT116, either lack LPA_5 or express at a low level [9,10].

The intestinal tract plays a critical role in immune system homeostasis. It was reported that LPA_2 is expressed in human $CD4^+$ T cells and $CD19^+$ B cells, but not in $CD8^+$ T cells [12]. A recent study showed that LPA_5 is highly expressed in the intraepithelial lymphocytes of mouse intestine, with the highest in $CD8^+$ T cells [13]. In addition, LPA_5 is abundantly expressed in human mast cells [14].

Role of LPA in CRC

CRC results from the accumulation of multiple independent genetic instabilities and activation of oncogenic pathways that transform epithelial cells to cancerous cells [15]. In addition, growth factors, angiogenic factors, and motility factors that are produced by the tumor cells or surrounding environment play a critical role in malignant transformation. A body of evidence supports that LPA is such a factor that stimulates proliferation, survival, and migration of malignant cells. ATX was originally identified as a motility factor from the culture supernatant of human melanoma cells [16]. Up-regulation of ATX in malignancies including breast ovarian, thyroid and lung cancer correlates with invasiveness and metastatic potential of cancer cells [8]. Similarly, ATX is highly expressed in infiltrating cells in human CRC tumor tissue in the submucosal layer. ATX expression shows a positive correlation with tumor angiogenesis in the early stage of CRC [17]. However, whether LPA levels are elevated in CRC patients is not known. Nevertheless, extracellular ATX enhances locomotion of Caco-2 and MDCK cells [18], and the pan-antagonist of ATX and LPA receptor BrP-LPA is shown to be effective in limiting liver metastasis of HCT116 cells [19].

Among the LPA receptors, LPA_2 provides a considerable pathophysiological relevance to cancer progression. The first observation of aberrant expression of LPA receptors in cancer came from the study by Goetzl et al. [20] that showed increased LPA_2 transcript expression in ovarian cancer cells. Shida et al. [21] have shown elevated expression of LPA_2 and concurrent decrease in LPA_1 expression in CRC patients. The altered expression of LPA_2 is a common occurrence in several colon cancer cell lines [11].

Much work has underscored the positive effect of LPA on cancer cell proliferation and migration. LPA promotes proliferation and migration of human colon cancer cells, including HCT116, LS174T, SW480, and LoVo, via LPA_2 or LPA_3 [22,23]. Hepatic metastasis of

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