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Colorectal cancer cells – proliferation, survival and invasion by lysophosphatidic acid

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Abstract

Colorectal cancer (CRC) develops through a series of genetic modifications that transforms normal colonic epithelium to an adenoma and then ultimately adenocarcinoma. A body of evidence suggests that lysophosphatidic acid (LPA) is a potent inducer of cancer progression at multiple levels. However, the pathological significance and mechanisms of LPA-mediated effects in the intestinal tract have only recently drawn interests. CRC cells have aberrant LPA receptor expression and LPA enhances proliferation, survival, and invasion of CRC cells, implying LPA and its signaling pathways as potential targets for anti-cancer therapies. The mechanisms of fostering CRC by LPA include dysregulation of transcription factors, activation of mitogen-activated protein kinases, pro-inflammatory cytokines, and angiogenic factors. This review provides a brief summary of recent advance on the effects of LPA on CRC cells.

Keywords

phospholipids; G protein-coupled receptor; colorectal cancer

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in men and women in the United States with an estimated 142,500 new cases and more than 51,000 deaths from CRC in 2010¹. About 50% of the population in North America, Western Europe, and Australia develops an adenomatous polyp by the age of 70 and 5% of an average person has life-time risk to develop CRC. Colorectal tumorigenesis is the result of a progressive transformation of epithelial cells in the luminal surface of the intestinal tract to cancerous cells (Fearon and Vogelstein, 1990). Herein, we briefly review how tumor cells are regulated by lysophosphatidic acid (LPA) and its cognate receptors.

G protein-couple receptors (GPCRs) are responsible for the signal transduction of a wide variety of ligands, including neurotransmitters, hormones, growth factors, and lipids (Dorsam

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¹American Cancer Society, <http://www.cancer.org/acs/groups/content/@nho/documents/document/acspc-024113.pdf>

and Gutkind, 2007). The aberrant expression of GPCRs and their autocrine and paracrine activation are frequently associated with a wide range of pathological conditions, including cancer, inflammation, obesity, diabetes, heart failure, hypertension, and mental disorders. Not surprisingly, at least one third and perhaps as many as half of current marketed therapeutic agents target GPCRs (Dorsam and Gutkind, 2007).

LPA is one of the simplest phospholipids consisting of fatty acyl chain, glycerol backbone, and phosphate group. LPA has been detected in various biological fluids, including serum, plasma, saliva, and seminal fluid (van Meeteren and Moolenaar, 2007, Choi et al., 2010). LPA production has been implicated in various pathological processes, such as cancer, fibrosis, inflammation, atherosclerosis, asthma, and obesity (van Meeteren and Moolenaar, 2007, Choi et al., 2010). At least two major pathways for production of bioactive LPA have been identified. One involves a secreted lysophospholipase D (lysoPLD), which converts lysophosphatidylcholine (lysoPLC) to LPA. In the second pathway, phosphatidic acid is deacylated by phospholipase A₁ (PLA₁) or PLA₂. LPA levels are regulated by the balance between synthesis by lysoPLD and PLA, reversible conversion to monoacyl glycerol by lipid phosphate phosphatase (van Meeteren and Moolenaar, 2007, Choi et al., 2010).

One explanation that LPA can evoke such diverse biological effects is its role as a ligand for several cell surface receptors. LPA mediates its biological effects through specific GPCRs, LPA₁, LPA₂, LPA₃, LPA₄/GPR23, and LPA₅/GPR92 (Figure 1) (Choi et al., 2010). The classical LPA receptors, LPA₁₋₃, belong to the endothelial cell differentiation gene (EDG) family of GPCRs. The recently identified LPA₄ and LPA₅ are related to the purinergic P2Y receptor family, indicating two distinct ancestries. The expression pattern of LPA receptors varies widely among different tissues and cell types (Choi et al., 2010). In mouse intestinal tract, LPA₁ and LPA₅ are most abundant LPA receptors, with LPA₂, LPA₃, and LPA₄ at significantly lower levels (Lin et al., 2010).

LPA receptors can couple to multiple G proteins, enabling them to regulate a range of downstream signaling pathways. Through G_q and G_i, LPA receptors stimulate multiple signaling cascades, including phospholipase C-β (PLC-β)/protein kinase C (PKC)/Ca²⁺, Ras–Raf–1–mitogen activated protein kinase (MAPK), and phosphoinositide 3-kinase (PI3K)/AKT, while inhibiting the adenylyl cyclase-cyclic AMP pathway (van Meeteren and Moolenaar, 2007, Choi et al., 2010). In addition, LPA-mediated stress fiber formation and focal adhesion assembly have been shown to be mediated by G_{12/13}–mediated activation of RhoA. The signaling pathways elicited by LPA receptors often appear to overlap, but recent studies using mice with targeted deletion of single or multiple LPA receptors showed that each of the LPA receptors has distinct genetic and biological properties (Choi et al., 2010).

LPA₂ contains a unique carboxyl terminal sequence that preferentially binds to Class I PDZ domains. Recent studies helped to identify a number of PDZ-containing proteins, including Na⁺/H⁺ exchanger regulatory factor 2 (NHERF2), membrane-associated guanylate kinase with inverted orientation-2 (MAGI-2), MAGI-3, neurabin, leukemia-associated RhoGEF (Rho guanine nucleotide exchange factor), and PDZ-RhoGEF (Oh et al., 2004, Yun et al., 2005, Yamada et al., 2005, Zhang et al., 2007b). These interacting proteins play a critical role in determining LPA₂-mediated cellular signaling. For instance, NHERF2 facilitates activation of PLCβ and induction of cyclooxygenase-2 (Cox-2) and interleukin-8 (IL-8) (Oh et al., 2004, Yun et al., 2005), whereas MAGI-3 potentiates activation of RhoA (Zhang et al., 2007b). LPA₂, moreover, interacts with non-PDZ proteins such as Siva-1 and TRIP6 that regulate LPA₂-mediated cell survival and migration (Lin and Lai, 2008).

2. Colorectal cancer cell origin and plasticity

Tumorigenesis of intestine proceeds through well defined clinical stages that are associated with characteristic mutations (Fearon and Vogelstein, 1990). Vogelstein and coworkers first proposed a multistep genetic model that has come to serve as a paradigm for CRC (Fearon and Vogelstein, 1990). The Wnt/ β -catenin cascade plays the single most dominant force in controlling fate of epithelial cells in the intestine and colon. An early transformation of epithelial cells involves a mutation in the adenomatous polyposis coli (Apc) or Axin2, or an activating mutation of β -catenin. Additional mutations that activate the K-Ras/BRAF pathway result in the growth of a small adenoma to clinically significant size (>1cm). Further acquisition of inactivating mutations of the transforming growth factor- β (TGF- β) confers additional malignant features to adenoma cells. The subsequent malignant transformation to adenocarcinoma is driven by additional mutations in p53 (Fearon and Vogelstein, 1990, Kinzler and Vogelstein, 1996). In addition to the genetic instability, the activation of growth factor pathways is common in the pathogenesis of CRC cells. The activation of Cox-2, epidermal growth factor, and vascular endothelial growth factor (VEGF) is associated with various stages of CRC development and the extent of disease progression (Markowitz and Bertagnolli, 2009).

Although the genetic origin of intestinal tumorigenesis is well understood, the origin of adenoma and its mode of expansion are less agreeable. In the intestine and colon, proliferating progenitors cells generated from stem cells populate the base of the crypts (Sancho et al., 2004). The progeny of stem cells move along the vertical axis of the crypt towards the crypt apex, while continuing to divide until they reach the mid-portion. Subsequently, the migrating cells stop dividing and instead differentiate into enterocytes, enterocrine cells, and goblets cells (Sancho et al., 2004). It is generally accepted that cancer cells are derived from normal stem cells. The malignant transformation of the stem cell population occurs at the base of intestinal crypts, and the transformed stem cells migrate and expand to occupy entire crypt; this is called the bottom-up model (Preston et al., 2003). On the other hand, the top-down model was proposed based on the observations that dysplastic cells are often found at the luminal surface of the crypt (Shih et al., 2001). In this model, the development of adenomas originates probably from late progenitors at the intercryptal zones at the surface of mucosae proceeding down toward the crypt base replacing normal epithelial cells. Recently, constitutively active Wnt signaling has allowed the identification of the cell of origin of adenomas as the Lgr5 (leucine-rich-repeat containing GPCR 5) stem cells (Barker et al., 2009).

3. Proliferation and survival of colorectal cancer cells: the functional effects of LPA

The homeostatic cycles of proliferation and apoptosis are fundamental mechanisms to maintain the intestinal mucosa integrity (Sancho et al., 2004). However, dysregulation of cell proliferation and apoptosis results in hyperplasia and tumorigenesis. LPA is a potent inducer of proliferation of cancerous cells. Activation of LPA₁ promotes proliferation of DLD1 human colon cancer cells (Shida et al., 2003). In HCT116 or LS173T cells, LPA₂ and LPA₃, but not LPA₁, mediate LPA-induced cell proliferation (Yang et al., 2005), suggesting that there is a cell-line difference in the relative importance of each LPA receptors in its ability to induce proliferation of human colon cancer cells.

A mutation in *Apc* results in accumulation of β -catenin in the nucleus where β -catenin activates genes, such as c-Myc and cyclin D1, that induce transformation of epithelial cells (Sancho et al., 2004). One mechanism by which LPA stimulates proliferation of colon cancer cells is through cross-talk with the Apc/ β -catenin pathway (Yang et al., 2005). However, LPA cannot induce nuclear translocation of β -catenin in cells with a mutation in *Apc* or β -catenin that

constitutively activates β -catenin (Zhang et al., 2007a). In such cells, LPA enhances cell proliferation by activation of the transcription factor Krüppel-like factor 5 (KLF5), which is highly expressed in the proliferating crypt cell population (Zhang et al., 2007a). The induction of KLF5 by LPA appears to be independent of the mutation status of Apc or β -catenin, but a recent study showed that KLF5 physically interacts with β -catenin to enhance the nuclear localization and transcriptional activity of β -catenin (McConnell et al., 2009). Therefore, LPA-induced translocation of β -catenin and induction of KLF5 might not necessarily be mutually exclusive.

Many cancer cells can avoid apoptosis because they have lost or can bypass check points that control cell cycle progression (Sancho et al., 2004, Kinzler and Vogelstein, 1996). LPA rescued untransformed rat intestinal epithelial IEC-6 cells from camptothecin-induced apoptosis by upregulation of Bcl-2 expression and prevention of Bax translocation into mitochondria (Deng et al., 2003). In addition, LPA protected Caco-2 human colon cancer cells from etoposide-induced apoptotic death by upregulation of Bcl-2 expression, phosphorylation of Bad, and prolonged activation of the extracellular signal regulated kinases, Erks (Rusovici et al., 2007). Deng et al. showed that intestinal injury induced by γ -irradiation was reduced by oral administration of the synthetic LPA analog octadecenyl thiophosphate in wild type or LPA₁-null mice, but not in LPA₂-null mice (Deng et al., 2007). These results collectively suggest that LPA acts as an anti-apoptotic factor by activating LPA₂-mediated signaling in colon cancer cells.

Cell migration is a fundamental process to achieve cellular functions, such as wound repair, cell differentiation, embryonic development, invasion, and metastasis of tumor cells (Sancho et al., 2004). LPA acts as a strong stimulator of cell migration that is essential for healing superficial epithelial injury and maintenance of barrier function (Sturm et al., 1999). LPA rapidly induces actin and focal adhesion kinase (FAK) levels and stimulates migration of intestinal epithelial cells (Hines et al., 2000). Moreover, LPA was effective in ameliorating intestinal epithelial injury in rats (Sturm et al., 1999). However, unchecked migration of cells can give rise to invasive or metastatic gastrointestinal diseases. LPA stimulates metastatic potentials of Caco-2 cells by enhancing actin polymerization and villin redistribution on the cell surface membrane of Caco-2 cells (Khurana et al., 2008). LPA acting on LPA₁ promotes adhesion and migration of DLD1 cells, whereas LPA₂ in WiDr and HT29 cells stimulates proliferation and secretion of angiogenic factors, suggesting a distinct role of LPA receptors in colon cancer cells. As a potential inducer of angiogenesis, the positive role of LPA₂ in secretion of VEGF is particularly intriguing as VEGF is frequently targeted by hypoxia-inducible factor-1 α (Lee et al., 2006).

4. Associated pathologies

An early indication that LPA could contribute to tumorigenesis came from studies showing that LPA increases tumor cell proliferation and motility (van Meeteren and Moolenaar, 2007, Choi et al., 2010). The presence of LPA at elevated levels in the ascites and plasma of ovarian cancer patients have heightened its pathological importance in cancer (Xu et al., 1998). A noteworthy development underscoring the importance of LPA in cancer is the finding that autotoxin (ATX), involved in tumor invasion, neovascularization and metastasis, has lysoPLD activity converting PLC to LPA (van Meeteren and Moolenaar, 2007). This established a causal link between ATX and tumor cell behaviors and established LPA as a key contributor to metastatic transformation.

Although whether LPA level is elevated in CRC is unknown, a recent study demonstrated the potent effect of LPA on CRC (Lin et al., 2009). The multiple intestinal neoplasia (Apc^{Min/+}) mouse carries a mutation in the Apc gene and typically develops ~30 polyps in the small

intestine (Sancho et al., 2004), but oral administration of LPA to $Apc^{Min/+}$ mice nearly doubled the number of polyps in the intestine (Lin et al., 2009). However, LPA did not induce adenomatous lesions in wild type mice, suggesting that LPA alone is not sufficient to cause intestinal cancer in the absence of genetic predisposition to develop cancer.

Among the LPA receptors, LPA_2 provides a considerable pathophysiological relevance to cancer progression. The aberrant expression of LPA_2 has been reported in ovarian and breast cancer (Goetzl et al., 1999). Human CRC tissues express LPA_2 at elevated levels compared with corresponding healthy colonic tissues (Shida et al., 2004). Concurrently, LPA_1 expression is lower in adenocarcinomas of the colon (Shida et al., 2004). The aberrant expression of LPA receptors is a common occurrence in several types of cancer and the resulting effects are likely be compounded by increased and decreased expression of individual LPA receptors (Yun et al., 2005).

Inflammation is a known risk factor for many common malignancies and patients with inflammatory bowel disease are at increased risk to develop CRC (Rhodes and Campbell, 2002). LPA has a robust effect on inflammatory responses. LPA induces expression of nuclear factor κB (NF- κB), IL-6, IL-8, IL-13, Cox-2, urokinase-type plasminogen activator (uPA), VEGF, and TGF- β in various cell types (Choi et al., 2010, van Meeteren and Moolenaar, 2007). Indeed, transgenic mice overexpressing ATX or each of LPA receptors, LPA_{1-3} , in mammary gland show increased levels of macrophage inflammatory protein 3 α (MIP-3 α) and VEGF prior to tumor development, suggesting that LPA contributes to tumorigenesis by increasing inflammatory responses (Liu et al., 2009).

The significance of LPA_2 in promotion of colitis-associated colon cancer was recently demonstrated using LPA_2 -null mice (Lin et al., 2009). The extent of colonic dysplasia and inflammation induced by the carcinogen azoxymethane and dextran sulfate sodium was markedly lessened in LPA_2 -null mice compared with wild-type mice (Lin et al., 2009). The reduced inflammation and dysplasia was accompanied by reduced cell proliferation, KLF5 and cox-2 expression, and infiltration of macrophages. Interestingly, the levels of monocyte chemoattractant protein 1 (MCP-1) and migration inhibitory factor (MIF) were markedly lower in LPA_2 -null mice than wild-type mice, although the direct relevance of MCP-1 or MIF to the decreased number of macrophages or inflammation is yet to be established.

The potential involvement of LPA in physiological and pathophysiological processes is enormous. Development of compounds inhibiting LPA signaling and LPA production are in progress and these inhibitors should help to tailor the therapeutic potential of targeting the LPA-mediated pathway. So is LPA all bad? Recent evidence has highlighted the physiological importance of LPA_2 to inhibit chloride secretion by the cystic fibrosis transmembrane conductance regulator as well as the role of LPA_5 in the stimulation of sodium absorption in mouse intestine (Li et al., 2005, Lin et al., 2010). These studies suggest that LPA and its analogues have a therapeutic potential against diarrheal diseases, and development and application of receptor specific agonists promise to provide a new therapeutic approach.

Cell Facts

- Colorectal cancer cells arise from multiple genetic mutations.
- Functional loss of Apc is an early event in colorectal tumor initiation.
- Cancer cells of the intestine and colon originate from crypt stem cells.
- Colorectal cancer cells have aberrant expression of LPA receptors.

- Colorectal cancer cells secrete pro-inflammation cytokines that further foster cancer progress.

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Figure 1. Signaling pathways in intestinal epithelial cells

LPA₁ regulates cell proliferation and migration. LPA₂ interacts with several PDZ proteins. LPA₂ is the major LPA receptor that regulates colon cancer cells. LPA acting LPA₃ shows significant involvement in migration and inflammation. In addition, LPA regulates electrolyte and fluid transport in the intestinal tract.