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Emerging roles of lysophosphatidic acid receptor subtype 5 (LPAR5) in inflammatory diseases and cancer

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Abstract

Lysophosphatidic acid (LPA) is a bioactive lipid mediator that regulates a variety of cellular functions such as cell proliferation, migration, survival, calcium mobilization, cytoskeletal rearrangements, and neurite retraction. The biological actions of LPA are mediated by at least six G protein-coupled receptors known as LPAR1–6. Given that LPAR1–3 were among the first LPARs identified, the majority of research efforts have focused on understanding their biology. This review provides an in-depth discussion of LPAR5, which has recently emerged as a key player in regulating normal intestinal homeostasis and modulating pathological conditions such as pain, itch, inflammatory diseases, and cancer. We also present a chronological overview of the efforts made to develop compounds that target LPAR5 for use as tool compounds to probe or validate LPAR5 biology and therapeutic agents for the treatment of inflammatory diseases and cancer.

Keywords

Lysophosphatidic acid; Lysophosphatidic acid receptor; Cancer; Inflammation; Tumor immunity; Wound healing

1. Introduction

Lysophosphatidic acid (LPA) is a simple lipid molecule comprised of a phosphate or a cyclic phosphate head group (designated as cyclic phosphatidic acid), a glycerol backbone, and a fatty acid or fatty alcohol chain. The ether analog is designated as alkyl glycerophosphate in IUPHAR nomenclature but commonly referred to as alkyl-LPA. LPA was originally discovered in urine as the Darmstoff and brain extracts in late 1950s (Kirschner & Vogt,

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1961; Vogt, 1957). However, it was not until the late 1980s that LPA research gained traction, when it was shown to regulate blood pressure *in vivo*, elicit calcium transients in fibroblasts, promote cell proliferation, activate oscillatory chloride current *via* a putative plasma membrane receptor in *Xenopus oocytes*, and induce neurite retraction *in vitro* (Jalink, van Corven, & Moolenaar, 1990; Moolenaar et al., 1986; Tigyi & Miledi, 1992; Tokumura, Fukuzawa, & Tsukatani, 1978; van Corven, Groenink, Jalink, Eichholtz, & Moolenaar, 1989).

Around the same time, evidence supporting a role for LPA in regulating wound healing began to emerge. The production of LPA was linked to platelet activation, leading to the presumption that it was released by thrombin-activated platelets (Eichholtz, Jalink, Fahrenfort, & Moolenaar, 1993; Gerrard & Robinson, 1989). Elevated levels of LPA were detected in the aqueous humor, brain, and cerebrospinal fluid (CSF) following corneal or cerebrovascular injury and in skin blisters (Crack et al., 2014; Liliom et al., 1998; Mazereeuw-Hautier et al., 2005; Tigyi et al., 1995). Furthermore, several studies showed that LPA treatment accelerated the closure of skin wounds in mice and rats and repaired intestinal epithelium damaged by either experimentally induced colitis or radiation (Balazs, Okolicany, Ferrebee, Tolley, & Tigyi, 2001; Demoyer, Skalak, & Durieux, 2000; Deng et al., 2002; Sturm, Sudermann, Schulte, Goebell, & Dignass, 1999). A growing list of cellular responses is mediated by LPA following tissue injury, including the proliferation and recruitment of fibroblasts and epithelial cells, vascular and extracellular matrix (ECM) remodeling, and modulation of the immune response (Balazs et al., 2001; Demoyer et al., 2000; English, Garcia, & Brindley, 2001; Goetzl & Rosen, 2004; Hadidi & Athanasiou, 2013; Jalink, Hordijk, & Moolenaar, 1994; Lee, Goetzl, & An, 2000; Olorundare, Peyruchaud, Albrecht, & Mosher, 2001; Panetti et al., 2001; Panetti, Chen, Misenheimer, Getzler, & Mosher, 1997; Sauer et al., 2004; Stortelers, Kerkhoven, & Moolenaar, 2008; Sturm et al., 1999; Tigyi, Dyer, & Miledi, 1994; Xu, Yin, & Yu, 2007; Zhao & Natarajan, 2013). These studies further establish LPA as a master regulator of the natural healing process.

Given the importance of LPA in wound healing, it is not surprising that dysregulation of this signaling pathway can cause chronic inflammation and promote cancer progression. Increased levels of LPA are found in the biological fluids of patients with ovarian or gastric cancer, idiopathic pulmonary fibrosis, rheumatoid arthritis, chronic liver or renal diseases, systemic sclerosis, multiple sclerosis, cardiovascular diseases and neuropathic pain (Baker et al., 2002; Balood et al., 2014; Kremer et al., 2010; Kurano et al., 2015; Kuwajima et al., 2018; Nochi et al., 2008; Sasagawa, Suzuki, Shiota, Kondo, & Okita, 1998; Tager et al., 2008; Tokumura et al., 2009; Wang et al., 2019; Watanabe et al., 2007; Xu et al., 1995; Zeng et al., 2017; Zhang et al., 2016). In each of these studies, the presence of high LPA levels has been linked to the pathological progression of the disease.

How LPA modulates such a broad spectrum of physiological and pathological responses has long piqued the interest of researchers. Over the last four decades, we learned that the biological responses of LPA are mediated through at least six G protein-coupled receptors (GPCRs) termed LPA receptors 1–6 (LPAR1–6), and intracellularly *via* the nuclear receptor peroxisome proliferator activated receptor gamma (PPARγ). LPAR1–3 belong to

the endothelial gene family of GPCRs, while LPAR4–6 are members of the P2Y purinergic family of GPCRs (Geraldo et al., 2021; Xiang, Lu, Shao, & Wu, 2020; Yung, Stoddard, & Chun, 2014). Different molecular species of LPA exist in biological fluids, each with varying fatty acid chain length and degree of saturation, with the fatty acid moieties able to be linked to the glycerol backbone at either the *sn-1* or *sn-2* position, resulting in 1-acyl- or 2-acyl-LPA species, respectively (Bandoh et al., 2000; Gerrard & Robinson, 1989; Tigyi & Miledi, 1992). Alternatively, an ether linkage, rather than an ester bond, can form at the *sn-1* position of the glycerol backbone, giving rise to 1-alkyl-LPA and 1-alkenyl-LPA (Fischer et al., 1998; Sugiura et al., 1999). Structure-activity relationship (SAR) studies revealed that LPARs have distinct preferences for different LPA species. When expressed in mammalian cells, LPAR1–3 showed preferential activation by 1-acyl-LPA species containing unsaturated fatty acids over their saturated analogs of the same hydrocarbon chain length (Fujiwara et al., 2005). Studies have proposed that 2-acyl-LPA with unsaturated fatty acids could be the preferred ligand for LPAR6, whereas alkyl-LPA is a more potent ligand at LPAR5 and PPARγ than acyl-LPA species (Davies et al., 2001; Inoue et al., 2011; Tsukahara et al., 2006; Williams et al., 2009; Yanagida et al., 2009). Not only do LPARs differ in their ligand specificities, but they also couple to different G proteins such as $G\alpha_s$, $G\alpha_i$, $G\alpha_q$ and $G\alpha_{12/13}$ (Fig. 1). Moreover, the expression profile of LPARs is cell type-specific and spatiotemporally regulated during embryonic development and pathological conditions (Geraldo et al., 2021; Xiang et al., 2020; Yung et al., 2014). These differences enable LPA to mediate a wide range of physiological and pathological responses.

In this review, we provide a brief overview of the pathways that regulate LPA production and degradation, followed by an in-depth discussion on the LPAR subtype 5 (LPAR5), which has recently emerged as a key player in modulating pathological conditions including pain, itch, cerebral inflammation, and cancer. Finally, we discuss some of the most recent developments on promising compounds that target LPAR5 as a therapeutic approach for treating inflammatory diseases and cancer.

2. LPA production and degradation pathways

Several pathways are involved in the biosynthesis of LPA (Fig. 2). First, lysophosphatidylcholine (LPC) is hydrolyzed by autotaxin (ATX), a secreted enzyme with lysophospholipase D activity, to generate LPA. The bulk of LPA in biological fluids is generated through this pathway, as mice heterozygous for the ATX gene (*Enpp2*$^{+/-}$) exhibit a 50% reduction in plasma LPA levels (van Meeteren et al., 2006). The second pathway involves the conversion of phosphatidic acid (PA) to LPA by membrane-associated PA-selective phospholipase A_1 enzymes (PA-$PLA_1\alpha$ and PA-$PLA_1\beta$) (Aikawa, Hashimoto, Kano, & Aoki, 2015). Relatively little is known about the cellular actions of LPA produced by PA-$PLA_1\alpha$ and PA-$PLA_1\beta$. Only two studies show that PA-$PLA_1\alpha$ preferentially generates 2-acyl LPA and is involved in hair follicle formation, and that PA-$PLA_1\beta$ is abundantly expressed in Ewing family tumors (Foell et al., 2008; Inoue et al., 2011). Additional intracellular enzymes involved in LPA production include glycerol-3 phosphate acyltransferase (GPAT), which converts glycerol-3 phosphate to LPA, and acylglycerol kinase (AGK), which converts monoacylglycerol (MAG) to LPA (Bektas et al., 2005).

Likewise, the breakdown of LPA is also mediated by several classes of enzymes, the most important of which are the lipid phosphate phosphatases (LPPs). Thus far, only three members of the LPP family of enzymes (LPP1–3) have been identified. They are localized to the plasma membrane, and membranes of the Golgi apparatus and endoplasmic reticulum, allowing them to hydrolyze both extra- and intracellular lipid phosphates (Tang & Brindley, 2020). LPA can also be converted to PA by LPA acyltransferases (LPAAT) and to glycero-3 phosphate by lysophospholipases (Baker & Chang, 1999; Thompson & Clark, 1994).

LPA levels are strictly regulated during embryonic development. In mice, deletion of enzymes such as ATX or LPP3 that are involved in the production or degradation of LPA resulted in embryonic death due to abnormal vascular and neural development (Escalante-Alcalde et al., 2003; Moolenaar, Houben, Lee, & van Meeteren, 2013; Tanaka et al., 2006; van Meeteren et al., 2006). Furthermore, overexpression of ATX can cause lethal vascular defects in mice during embryogenesis (Yukiura, Kano, Kise, Inoue, & Aoki, 2015). Interestingly, the majority of ATX activity in adult mice is not required to maintain normal physiological homeostasis. Specifically, genetic deletion of *Enpp2* in adult mice resulted in >80% reduction in plasma LPA levels, which was well-tolerated (Katsifa et al., 2015). This finding is consistent with the lack of an obvious phenotype in *Enpp2*$^{+/-}$ heterozygous mice that exhibit a 50% reduction in plasma LPA levels (van Meeteren et al., 2006). It is possible that residual levels of ATX-derived LPA, combined with LPA produced by other biosynthetic pathways, are sufficient to sustain normal tissue homeostasis (Ninou, Magkrioti, & Aidinis, 2018).

It is worth noting that LPA can inhibit ATX expression, implying the presence of a self-regulating mechanism to ensure that LPA levels do not fluctuate aberrantly (Benesch, Zhao, Curtis, McMullen, & Brindley, 2015). Nevertheless, the presence of inflammatory factors can override this self-regulating mechanism. For example, ATX expression can be induced by lipopolysaccharide (LPS), tumor necrosis factor (TNFα), interleukins (IL-1β or IL-6) and type 1 interferons (IFNα or IFNβ), which could explain the elevated levels of ATX and LPA observed during inflammation (Benesch et al., 2015; Castelino et al., 2016; Li & Zhang, 2009; Nikitopoulou et al., 2012; Song, Guan, Zhao, & Zhang, 2015; Wu et al., 2010). If left unresolved, this could lead to the development of chronic inflammatory diseases and promote cancer progression. Indeed, aberrant expression of ATX, LPARs and/or LPPs is linked to the pathological progression of chronic inflammatory diseases and a variety of cancers including ovarian, breast, lung, prostate, pancreas, colon, melanoma, liver, and brain (Balijepalli, Sitton, & Meier, 2021; Magkrioti et al., 2019).

3. LPAR5 signaling

The majority of research efforts have been devoted to understanding the biology of LPAR1–3, which were among the first LPARs to be identified, as reviewed by (Geraldo et al., 2021; Xiang et al., 2020; Yung et al., 2014). However, growing evidence from the last decade suggests important roles for LPAR5 in modulating inflammatory diseases and cancer. LPAR5 was discovered in 2006 by two independent groups using distinct screening approaches that resulted in the deorphanization of GPR92. They found that LPAR5 shares 22% amino acid identity with LPAR1–3 and ~35% similarity with LPAR4 (Kotarsky et al.,

2006; Lee, Rivera, Gardell, Dubin, & Chun, 2006). LPAR5 can be activated by not only LPA, but also natural lipid analogs including cyclic phosphatidic acid, farnesyl phosphate, farnesyl pyrophosphate, and anandamide phosphate. SAR studies highlighted that the ligand preferences of LPAR5 are different than those of LPAR1–3, with the order of potency of LPAR5 ligands being alkyl-LPA > acyl-LPA > farnesyl phosphates ≥ *N*-arachidonylglycine (Williams et al., 2009). In humans, LPAR5 is predominantly expressed in the heart, placenta, spleen, brain, lung, and gut, while in mice, it is expressed in the small intestine, stomach, spleen, skin, thymus, lung, and the developing brain up to embryonic day E12.5 (Kotarsky et al., 2006; Lee et al., 2006; Oh et al., 2008; Ohuchi et al., 2008). However, LPAR5 expression in the mouse brain was not detected between days E16 and postnatal day 30 (Suckau et al., 2019). Whether this temporal expression of LPAR5 in the developing brain has any biological significance remains to be investigated.

In terms of cellular functions, LPAR5 activates $G\alpha_{q/11}$ to promote Ca^{2+} mobilization and inositol phosphate production and $G\alpha_{12/13}$ to regulate neurite retraction and stress fiber formation (Lee et al., 2006; Oh et al., 2008). Activation of LPAR5 also increases cAMP levels, although this appears to be mediated by the G protein βγ subunits rather than the $G\alpha_s$ subunits (Kotarsky et al., 2006; Lee et al., 2006; Oh et al., 2008). LPAR5 has been shown to induce β-Arrestin recruitment. Whether the recruitment of β-Arrestin by LPAR5 participates in additional downstream signaling events other than signal termination via receptor internalization remains to be determined (Kroeze et al., 2015; Yin et al., 2009). Interestingly, *Lpar5*$^{-/-}$ knockout (KO) mice develop normally but exhibit behavioral abnormalities relative to wildtype (WT) mice. The *Lpar5*$^{-/-}$ KO mice were less anxious, displayed reduced fear responses, and were hyperactive at night. *Lpar5*$^{-/-}$ KO mice also outperformed WT mice in several motivational-driven tasks, suggesting that LPAR5 signaling may be involved in psychopathology (Callaerts-Vegh, Leo, Vermaercke, Meert, & D'Hooge, 2012).

4. Role of LPAR5 in modulating platelet function

In response to injury, platelets are among the first cells to become activated to initiate hemostasis and tissue repair (Etulain, 2018). As noted previously, LPA was presumed to be released when platelets are activated (Eichholtz et al., 1993; Gerrard & Robinson, 1989). However, activated platelets actually generate LPA in a two-step process: first by secreting phospholipases including group IIA secretory PLA_2 ($sPLA_2$-IIA) and phosphatidylserine-specific PLA_1 (PS-PLA_1) that convert membrane phosphospholipids to various lysophospholipids including LPC, lysophosphatidylethanolamine, and lysophosphatidylserine. Second, these lysophospholipids are hydrolyzed by ATX to produce LPA (Aoki et al., 2002; Bolen et al., 2011; Sano et al., 2002).

LPA induces human platelet shape change, aggregation, and co-adhesion to monocytes, suggesting that LPA signaling may be involved in the pathological activation of platelets during thrombosis (Haseruck et al., 2004; Simon, Chap, & Douste-Blazy, 1982; Tokumura et al., 2002). This is supported by the discovery that LPA is produced during the mild oxidization of low-density lipoprotein (Kurano et al., 2015; Siess et al., 1999). High levels of LPA were detected subsequently in the lipid-rich core of human and mouse atherosclerotic plaques, with alkyl-LPA species accounting for 20% of total LPA species detected (Bot et

al., 2010; Rother et al., 2003; Siess et al., 1999). Moreover, platelets isolated from patients with coronary artery disease were more responsive to LPA than were those from healthy donors. However, the effect of LPA on platelet aggregation in healthy donors varies, with approximately 20% of donors being nonresponsive to LPA stimulation (Haseruck et al., 2004; Pamuklar et al., 2008). Gene expression profiling showed that LPAR4, LPAR5 and PPARγ were expressed abundantly in human platelets, whereas LPAR1 and LPAR2 were less abundantly expressed (Amisten, Braun, Bengtsson, & Erlinge, 2008; Rowley et al., 2011; Spinelli et al., 2008). Interestingly, increased expression of LPAR4 and PPARγ was detected in platelets from nonresponsive donors, suggesting that LPA may act *via* LPAR4 and/or PPARγ to mediate inhibitory signals that block platelet aggregation in humans (Pamuklar et al., 2008). In fact, activation of PPARγ by both synthetic and endogenous ligands such as rosiglitazone and 15d-PGJ2, respectively, has been shown to block activation of human platelets by collagen (Moraes et al., 2010).

The discovery that human platelets express LPAR5 and that alkyl-LPA is more potent than acyl-LPA in inducing platelet aggregation suggests that LPAR5 is most likely the receptor involved in platelet activation (Simon et al., 1982; Tokumura et al., 2002). Indeed, siRNA-mediated knockdown of LPAR5 in two human megakaryocytic cell lines abolished LPA-induced platelet shape change and aggregation (Khandoga, Pandey, Welsch, Brandl, & Siess, 2011). Similar findings were obtained when isolated human platelets were treated with LPAR5 antagonists (H2L 5987411 and H2L 5765834) (Williams et al., 2009). Although these studies confirmed that LPAR5 is the receptor responsible for LPA-mediated activation of human platelets, this is not the case in mouse platelets. LPA failed to induce murine platelet aggregation and prevented platelet aggregation induced by other agonists such as thrombin and adenosine diphosphate. Moreover, transgenic mice that overexpress ATX (*Enpp2-Tg*) exhibit elevated levels of circulating LPA and are more prone to bleeding than WT mice (Pamuklar et al., 2009). Transcriptomic analysis revealed that murine platelets express LPAR4 and do not express LPAR1–3, LPAR5, or PPARγ (Rowley et al., 2011). This may in part explain the observed differences in regulation of platelets by LPA in humans and mice (Fig. 3). These distinctions should be considered when using mouse models to study the role of LPA in regulating platelet function in cardiovascular diseases, inflammatory diseases, and cancer.

5. Role of LPAR5 in regulating neuropathic pain

The role of LPA signaling in modulating neuropathic pain was first reported to be mediated by LPAR1. *Lpar1*$^{-/-}$ KO mice were protected from neuropathic pain caused either by a single intrathecal injection of LPA or by partial sciatic nerve ligation (PSNL). Specifically, WT mice exhibited demyelination of the dorsal root ganglion (DRG) neurons, mechanical allodynia, and hyperalgesia while *Lpar1*$^{-/-}$ KO mice did not (Inoue et al., 2004). Subsequently, it was discovered that *Lpar3*$^{-/-}$ KO mice exhibited a blockage in the feed-forward mechanism of LPA accumulation following nerve injury and were thereby protected from neuropathic pain (Ma et al., 2009; Ueda, 2020). This is consistent with the observation that increased levels of LPA correlate significantly with pain intensity in patients with neuropathic pain (Kuwajima et al., 2018).

LPAR5 is also abundantly expressed in the DRG and dorsal horn neurons, where it may play a role in modulating pain signals (Lin, Rivera, & Chun, 2012; Oh et al., 2008). Indeed, *Lpar5*$^{-/-}$ KO mice were protected from developing neuropathic pain caused by PSNL and multiple sclerosis (Lin et al., 2012; Tsukahara et al., 2018). Interestingly, the mechanism by which LPAR5 modulate pain signals is distinct from that of LPAR1. In response to nerve injury, LPAR1 causes demyelination of the DRG neurons, upregulation of neuropathic pain markers (calcium channel $Ca\alpha_2\delta_1$, ephrinB1, and PKCγ), and reorganization of Aβ fiber-mediated signal transmission (Inoue et al., 2004; Lin et al., 2012; Xie, Matsumoto, Chun, & Ueda, 2008). These events were not observed in *Lpar5*$^{-/-}$ KO mice subjected to PSNL. Instead, nerve injury in the spinal cord dorsal horn of *Lpar5*$^{-/-}$ KO mice resulted in significant reduction in the phosphorylation of cAMP response element binding protein (pCREB), a known mediator of neuropathic pain. Since LPAR1 and LPAR5 have opposing effects on cAMP signaling, it is possible that an increase in cAMP accumulation *via* LPAR5 could result in pCREB activation in this scenario, leading to the development of neuropathic pain (Lin et al., 2012) (Fig. 4).

Aside from neuropathic pain, *Lpar5*$^{-/-}$ KO mice exhibit some degree of reduced sensitivity to acute pain compared to WT mice. However, significance differences in pain sensitivity between genotypes were observed in the tail withdrawal latency test, but not in the hot plate and Hargreaves' tests. *Lpar5*$^{-/-}$ KO mice also recovered faster from inflammatory pain caused by complete Freund's adjuvant, whereas no differences were observed when formalin or carrageenan were used as pain-inducing stimuli (Callaerts-Vegh et al., 2012). This is in contrast to the results of a recent study in which induction of pain by formalin, carrageenan, and prostaglandin E2 (PGE_2) was significantly reduced by the LPAR5 antagonist Cpd3/UA02085 (Langedijk et al., 2022). Whether the differences between the two studies were due to the different mouse strains used in the *in vivo* experiments remains to be determined.

6. Role of LPAR5 in regulating itch

LPA was identified in the serum of patients with cholestatic pruritus as an itch factor that induces mobilization of intracellular Ca^{2+} in neuronal cells. The levels of ATX in cholestatic serum was found to correlate positively with itch intensity (Kremer et al., 2010). Furthermore, intradermal injection of LPA induced scratch responses in mice in a dose-dependent manner (Hashimoto, Ohata, & Momose, 2004; Shimizu et al., 2014). However, the mechanism by which LPA causes itch remains unclear. In one study, this effect was mediated in part by activation of LPAR1 (Shimizu et al., 2014), while another showed that genetic silencing or pharmacological inhibition of LPAR5 with the antagonist TCLPA5–4 abolished LPA-induced Ca^{2+} mobilization in neuronal cells. The authors found that LPAR5 was involved in a feed forward mechanism that promotes the intracellular production of LPA *via* the actions of phospholipase D and Ca^{2+}-independent $iPLA_2$. The resultant intracellular LPA activates transient receptor potential ankyrin 1 (TRPA1) and vanilloid 1 (TRPV1) to induce itch sensations (Kittaka, Uchida, Fukuta, & Tominaga, 2017). This mechanism differs from previous research that found that extracellular LPA was transported intracellularly to activateTRPV1 to induce pain (Nieto-Posadas et al., 2011). Interestingly, both LPAR5 and LPAR1 colocalize with TRPV1 in DRG neurons and activation of LPAR1 potentiated TRPV1 signals *via* a PKCε-dependent pathway (Oh et al., 2008; Pan, Zhang, &

Zhao, 2010). Thus, further studies are needed to clarify the crosstalk between the LPAR1, LPAR5, and TRPV1 signaling pathways that mediates the sensations of itch and pain (Fig. 5).

Unexpectedly, treatment of mice with the LPAR5 antagonist Cpd3/UA08125 increased their scratch responses to itch in a manner that was independent of TRPA1 and TRPV1 activation (Langedijk et al., 2022). Although Cpd3/UA08025 was previously reported to be a selective antagonist of LPAR5, we found it to be also a potent antagonist of LPAR4 (Kozian et al., 2016; Lee et al., 2020). Thus, it is unclear whether the itch sensation observed in mice treated with Cpd3/UA08025 is caused by inhibition of LPAR5 or LPAR4. More research is needed to address the disparities in the findings of these studies.

7. Role of LPAR5 in regulating cerebral inflammation

As noted previously, LPA levels are increased in the CSF of patients with traumatic brain injury and in the plasma of patients with ischemic cerebrovascular disease (Crack et al., 2014; Li et al., 2008). In mice challenged with transient middle cerebral artery occlusion (tMCAO), increased expression of LPAR5 was observed in activated microglia in the ischemic core (Sapkota, Lee, Park, & Choi, 2020). Microglia are macrophage-like cells that reside in the central nervous system (CNS) and play essential roles in brain development, immune surveillance, and tissue repair. Like peripheral macrophages, microglia have both pro- and anti-inflammatory activities and their dysfunction is linked to neuroinflammatory and neurodegenerative diseases (Bachiller et al., 2018). Activation of LPAR5 induces a proinflammatory and promigratory signature in microglia that is potentially neurotoxic, which may contribute to the pathogenesis of CNS disorders (Plastira et al., 2016; Plastira et al., 2017; Sapkota et al., 2020). Specifically, LPAR5 activates the protein kinase D pathway, resulting in the phosphorylation of downstream transcription factors such as NFκB, STAT1, STAT3, and c-Jun. The majority of these transcription factors drive inflammation by increasing the expression of cytokines (TNFα, IL-1β, and IL-6) and chemokines (CXCL10, CCL5 and CXCL2) and by producing nitric oxide and reactive oxygen species (Plastira et al., 2016; Plastira et al., 2017; Plastira et al., 2019; Plastira et al., 2020). Following brain injury or cerebral ischemia, persistent accumulation of these factors causes neurotoxicity and brain damage (Fig. 6).

Indeed, when mice challenged with tMCAO were treated with the LPAR5 antagonist TCLPA5–4, they exhibited reduced accumulation of proinflammatory microglia in the ischemic core. An overall reduction in neuroinflammation and neuronal cell death was also observed in mice treated with TCLPA5–4 (Sapkota et al., 2020). The role of LPAR5 in promoting neuroinflammation caused by LPS-induced peripheral endotoxemia was investigated in mice treated with the novel LPAR5 antagonist AS2717638, which were protected from neuroinflammation (Joshi et al., 2021). This observation was further validated in *Lpar5*$^{-/-}$ KO mice, which exhibited circulating levels of TNFα and IL-1β that were significantly lower than those in WT mice. Moreover, the expression of IL-6 and CXCL2 was significantly reduced in the brain of *Lpar5*$^{-/-}$ KO mice treated with LPS (Joshi et al., 2022). The discovery that LPAR5 signaling plays an important role in modulating

microglia function may open up new avenues of research in areas such as neurodegenerative diseases in which microglia dysfunction has been implicated.

8. Role of LPAR5 in cancer

LPAR5 regulates cancer cell proliferation, migration, invasion, and tumor immunity. LPAR5 expression is upregulated in human non-small-cell lung carcinoma (NSCLC) and human papillary thyroid carcinoma (PTC) compared to their respective normal tissues (Wu et al., 2020; Zhang, Chen, & Xu, 2020; Zhao et al., 2021). Overexpression of LPAR5 in NSCLC positively correlates with a higher incidence of metastasis and poor prognosis. ShRNA-mediated knockdown of LPAR5 in several human NSCLC cell lines reduced cell proliferation and migration *in vitro* and tumor growth *in vivo*, further confirming the protumorigenic role of LPAR5 in NSCLC (Zhang et al., 2020). Likewise, LPAR5 promotes the proliferation, migration, and invasion of human PTC cells *in vitro* and treatment with TCLPA5–4 significantly decreases growth of PTC xenografts in nude mice (Wu et al., 2020; Zhao et al., 2021). Recently, LPAR5 was identified as a key regulator of radiation-induced epithelial-to-mesenchymal transition (EMT) in human cervical (HeLa) and lung (A549) cancer cells. Specifically, radiation upregulated LPAR5 expression in a bidirectional manner, with downregulation occurring between 2 and 4 h after irradiation and upregulation occurring 24 h later. Upregulation of LPAR5 at the 24-h time point was linked to increased expression of EMT markers such as Snail, matrix metalloproteinase 1 (MMP1) and MMP9, while siRNA-targeted knockdown of LPAR5 abolished their expression. The authors proposed that the increase in EMT markers induced by LPAR5 could make cancer cells more radioresistant (Sun et al., 2022). Contrary to these findings, LPAR5 serves as a negative regulator of cell migration and invasion in human sarcoma cell lines (HOSL5 and HT1080L5) by a mechanism that involves the downregulation of MMP2 and MMP9 (Dong et al., 2014). Likewise, activation of LPAR5 by LPA inhibits the migration and invasion of murine B16-F10 melanoma cells *in vitro* (Jongsma, MatasRico, Rzadkowski, Jalink, & Moolenaar, 2011; Lee et al., 2015). The underlying mechanism is mediated by decreased PIP3 signaling together with an increase in cAMP accumulation and activation of the protein kinase A pathway (Jongsma et al., 2011). Taken together, these findings suggest that LPAR5 signaling can mediate opposing cellular effects depending on the type of cancer.

Perhaps the most intriguing aspect of LPAR5 signaling in cancer is its role in regulating tumor immunity. Early reports revealed that CD8 T cells isolated from the small intestines of mice primarily expressed LPAR5, followed by LPAR2 and LPAR1 (Kotarsky et al., 2006). Subsequently, naïve CD8 T cells isolated from mouse spleen or human blood were found to express LPAR5, LPAR6 and LPAR2 (Mathew et al., 2019; Oda et al., 2013). Interestingly, LPAR5 was found to serve as an inhibitory receptor that repressed T cell receptor (TCR) signaling in human and mouse cells. In particular, activation of LPAR5 by LPA impeded antigen specific TCR-induced Ca^{2+} mobilization, T cell activation, proliferation, and cytotoxic effector functions (Mathew et al., 2019; Oda et al., 2013). LPA also hampered the formation and function of immunological synapses by reprogramming the cytoskeletal dynamics and disrupting the localization of at least three key signaling molecules, namely RhoA, mDia1, and IP3R1. However, the LPAR responsible for mediating this process remains unknown (Kremer et al., 2022). Nevertheless, all of these events could

lead to an impaired antitumor immune response. This hypothesis was validated in several *in vivo* experiments showing firstly that CD8 T cells lacking LPAR5 expression were more effective at reducing the growth rate of B16-F10 melanoma and EG7 lymphoma tumors in mice than WT CD8 T cells (Mathew et al., 2019; Oda et al., 2013). Secondly, *Lpar5* $^{-/-}$ KO mice exhibited an 85% reduction in B16-F10-derived lung metastasis relative to their WT littermates (Lee et al., 2015). Notably, robust CD8 T cell infiltration was observed in the few lung metastasis that developed in *Lpar5*$^{-/-}$ KO mice (Lee et al., 2020). These studies highlight a distinct role for LPAR5 as an immune checkpoint receptor expressed in CD8 T cells to modulate tumor immunity (Fig. 7).

Further transcriptomic analysis of immune cells isolated from the ascites fluid of ovarian cancer patients revealed that tumor associated macrophages (TAM) express ATX, LPAR5 and LPAR6 (Reinartz et al., 2019). TAM in osteosarcoma tumors also express high levels of LPAR5, which positively correlates with expression markers for phagocytosis and antigen presentation (He et al., 2022). Although LPA promotes the conversion of circulating monocytes to macrophages *via* activation of PPARγ, the role of LPAR5 in regulating the function of macrophages or TAM in the context of cancer is largely unknown (Ray & Rai, 2017). However, an *in vivo* model of murine psoriasis was used to show that LPAR5 induces activation of the NLRP3 inflammasome in macrophages, causing the production of proinflammatory cytokines. Treatment with TCLPA5–4 improved psoriasis symptoms and reduced the infiltration of macrophages into skin lesions (Gaire et al., 2020).

LPAR5 is also highly expressed in human mast cells. Activation of LPAR5 by LPA causes mast cells to release macrophage inflammatory protein-1β (MIP-1β), a potent activator and chemoattractant for many immune cells including monocytes, macrophages, dendritic cells, and lymphocytes (Lundequist & Boyce, 2011). Likewise, LPAR5 and LPAR2 are abundantly expressed in B cells. Activation of LPAR5 by LPA inhibits antigen specific BCR-induced Ca^{2+} mobilization and subsequent antibody production, suggesting that LPAR5 signaling may be involved in impeding humoral immune responses (Hu et al., 2014). While the observation that LPAR5 is abundantly expressed in many different immune cell types is certainly exciting, more research is needed to fully comprehend its significance in the context of inflammatory diseases and tumor immunity.

9. Role of LPAR5 in regulating intestinal epithelial cell repair

The gastrointestinal (GI) tract is lined with a layer of enterocytes responsible for nutrient absorption and formation of a physical and chemical barrier to protect the host from harmful contents in the GI lumen. LPAR1, LPAR2 and LPAR5 are abundantly expressed in the intestinal epithelium, where they regulate a wide range of cellular functions (Lee et al., 2013). For example, LPAR1 promotes the proliferation and migration of rat intestinal epithelial cells (IEC-6) *via* a PLCβ-dependent pathway. The authors found that both the number of proliferating enterocytes in the crypts and the rate of enterocytes migration along the crypt-villus axis were significantly reduced in *Lpar1*$^{-/-}$ KO mice relative to WT or *Lpar2*$^{-/-}$ KO mice. Furthermore, LPA treatment accelerated intestinal wound closure in WT mice but not in *Lpar1*$^{-/-}$ KO mice, suggesting that LPAR1 may play an important role in wound repair (Lee et al., 2013).

LPA also protects IEC-6 cells from apoptosis induced by serum withdrawal, chemotherapy, and radiation (Deng et al., 2002). The protection from radiation-induced apoptosis is mediated by LPAR2, since *Lpar2*$^{-/-}$ KO mice were more susceptible to radiation-induced death than WT or *Lpar1*$^{-/-}$ KO mice (Deng et al., 2007). At least four key events occur upon activation of LPAR2 (Fig. 8A). First, the unique C terminus of LPAR2 contains LIM- and PDZ-binding domains that form a ternary macromolecular complex with thyroid receptor-interacting protein 6 (TRIP6) and Na\\H exchange response factor (NHERF2). This macromolecular signaling complex promotes the long-lasting activation of prosurvival signaling pathways such as ERK1/2 and AKT. Second, LPAR2 can bind to the pro-apoptotic mediator SIVA1 and target it for polyubiquitination and subsequent proteasomal degradation (E, et al., 2009). Third, radiation increases the expression of ATX and LPAR2, indicating the presence of a feed-forward protective mechanism that amplifies LPA signaling. Fourth, activation of LPAR2 accelerates the resolution of phosphorylated γH2AX, which aids in DNA repair (Balogh et al., 2015). All four events contribute to the protection of cells from apoptosis caused by genotoxic stress. Recently, we found that the Lgr5-positive intestinal stem cells (Lgr5^{+} ISC) that maintain the continuous renewal of the intestinal epithelium express LPAR2. We showed that the LPAR2 agonist radioprotectin-1 protected Lgr5^{+} ISC from radiation-induced apoptosis *in vitro* and protected mice from radiation-induced death (Kuo et al., 2018).

Although LPAR5 is highly expressed in the intestinal epithelium, its role in regulating GI functions has been investigated only recently. Surprisingly, inducing global deletion of *Lpar5* (*Lpar5*^{iKO}) in adult mice causes significant intestinal inflammation, crypt ablation, weight loss, diarrhea, and mortality by day 11 (Liang, He, Han, & Yun, 2022) (Fig. 8B). The loss of intestinal crypts in *Lpar5*^{iKO} mice was further confirmed using cultured enteroids, in which deletion of *Lpar5* results in the loss of epithelial integrity, increased enterocyte apoptosis, and an overall reduction in growth compared to enteroids from WT mice. Similar results were obtained on treatment of WT enteroids with TCLPA5–4, suggesting that LPAR5 plays an essential role in the survival and growth of enteroids. Moreover, deletion of *Lpar5* in Lgr5^{+} ISC significantly decreased the number of crypts *in vivo*, suggesting that LPAR5 is required for the maintenance and renewal of ISC (Liang & Yun, 2022).

Nonetheless, the severe GI phenotype observed in *Lpar5*^{iKO} is strikingly different from that seen in constitutive or germline *Lpar5*$^{-/-}$ KO mice whose GI functions are normal. This suggests that a compensatory mechanism may be present in *Lpar5*$^{-/-}$ KO mice to maintain normal GI functions. Using a model in which *Lpar5* is constitutively deleted only in enterocytes (i.e., *Villin-Cre*; *Lpar5*$^{f/f}$ or *Lpar5*^{cKO} mice), the authors found that LPAR2 and LPAR3 were significantly upregulated in *Lpar5*^{cKO} enterocytes. Pharmacological inhibition of LPAR2 with H2L 5186303 significantly impaired the growth of *Lpar5*^{cKO} enteroids. However, no effect was observed when LPAR3 was inhibited by the LPAR1/3 antagonist Ki16425, suggesting that LPAR2 compensates for the loss of LPAR5 function (Liang & Yun, 2022). Akt phosphorylation decreases after LPAR2 inhibition in *Lpar5*^{cKO} enteroids, implying that LPAR2 may maintain the growth of *Lpar5*^{cKO} enteroids *via* the PI3K/AKT pathway. These *in vitro* findings were confirmed *in vivo* when *Lpar5*^{cKO} mice were treated with the LPAR2 antagonist H2L 5186303, which increased enterocyte apoptosis. Interestingly, expression of LPAR5 and LPAR3 is upregulated in enteroids isolated from

Lpar2$^{-/-}$ KO mice, suggesting that a similar compensatory mechanism also may exist in *Lpar2*$^{-/-}$ KO mice. Indeed, pharmacological inhibition of LPAR5 with AS2717638 substantially reduces the growth of enteroids from *Lpar2*$^{-/-}$ KO mice, whereas a moderate effect was observed when the LPAR1/3 antagonist Ki16425 was used (Liang & Yun, 2022). It is worth noting that the majority of these studies were conducted under basal or normal conditions. Nevertheless, the discovery that LPAR2 and LPAR5 may have overlapping functions in the basal maintenance of intestinal epithelium certainly raises the question of whether this compensatory mechanism exists during genotoxic insults or pathological conditions (Fig. 8C). Although H2L 5186303 is a more potent antagonist of LPAR2, it also can inhibit LPAR3 at low micromolar concentrations (Fells et al., 2008). Furthermore, we recently verified that H2L 5186303 also blocked LPAR5-mediated Ca^{2+} mobilization at low micromolar concentrations (unpublished data). More research will be needed to investigate this phenomenon.

10. Development of antagonist targeting LPAR5

Based on the mounting evidence that implicates LPAR5 in various inflammatory diseases and cancer, considerable efforts have been made to develop LPAR5 antagonists. Two compounds, H2L 5987411 and H2L 5765834 were identified from an in-silico screening of the Hit2Lead database using a pharmacophore model of LPAR5. H2L 5987411 served as a partial antagonist of both LPAR5 and LPAR4, whereas H2L 5765834 had antagonistic effects on LPAR1 > LPAR5 > LPAR3. Both compounds inhibit LPA-induced human platelet aggregation *in vitro* (Williams et al., 2009).

Subsequently, the non-lipid small molecule inhibitor diphenyl pyrazole carboxylic acid (TCLPA5–4) was identified by a high-throughput screening campaign as a selective antagonist of LPAR5. TCLPA5–4 inhibits LPA-mediated Ca^{2+} mobilization in RH7777 cells that stably express LPAR5 and inhibits LPA-induced aggregation of human platelets. Moreover, TCLPA5–4 exhibits no off target effects at high micromolar concentrations when screened against >80 other drug targets, with the notable exception of one protease (Kozian et al., 2012).

A more potent derivative of TCLPA5–4 was later synthesized and designated Cpd3/UA08025. This compound inhibits LPA-mediated Ca^{2+} mobilization and the release of monocyte chemoattractant protein 1 from the HMC-1 human mast cell line. Although the authors reported that this compound had no effect when screened against LPAR1–3 at 10 μM, no detailed information regarding the type of cells or the assay was provided (Kozian et al., 2016). As mentioned previously, we found that Cpd3/UA08025 is a more potent antagonist of LPAR4 than LPAR5 when tested in the Ca^{2+} mobilization assay using cells that stably express the respective receptor (Lee et al., 2020).

An orally bioavailable selective LPAR5 antagonist termed AS2717638 was identified. This compound inhibited LPA-induced accumulation of cAMP in CHO cells that stably express human LPAR5. The selectivity of AS2717638 for LPAR1–3 was determined in cells that overexpress the respective human LPAR using Ca^{2+} assays. However, its activity was not verified against LPAR4 and LPAR6, which share higher homology with LPAR5 than with

LPAR1–3. Nonetheless, the therapeutic utility of AS2717638 as an analgesic was evaluated in both mice and rats in which mechanical allodynia was induced by intrathecal injections of LPA, PGE_2 or (S)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). In all of the pain models tested, AS2717638 significantly reduced allodynia in WT but not in *Lpar5*$^{-/-}$ KO mice, confirming that the effect is mediated by LPAR5 (Murai et al., 2017). A summary of the IC_{50} values along with the assays that were used for target validation are listed for each compound in Table 1.

11. Conclusions

Despite significant advances in our understanding of LPAR5 biology in both physiology and pathophysiology, many of the molecular mechanisms underlying the cellular functions mediated by LPAR5 remain unknown. While we are beginning to comprehend the role of LPAR5 in modulating the immune response of T lymphocytes in the context of cancer, its role in inflammatory diseases has not yet been evaluated. Similarly, while LPAR5 appears to modulate macrophage and microglia functions by driving proinflammatory signals in these cells and affecting the healing process of skin lesions and brain injury, respectively, their role in cancer remains unknown. There is a gap in our knowledge as to whether LPAR5 is expressed by other immune cell types, such as dendritic cells, natural killer T cells, neutrophils, and myeloid-derived suppressor cells and if so, what its function(s) may be. In light of the recent discovery that LPAR2 and LPAR5 may compensate for one another in maintaining intestinal homeostasis, this begs the question of whether such overlapping function with other LPARs exists under physiological and pathophysiological conditions. Although germline or constitutive gene knockout mice models are useful for identifying genes required for embryo development and determining the functional roles of specific genes in pathophysiology, the fact that these models can potentially mask compensatory mechanisms in animals with no overt phenotype reminds us that all models have limitations and that the inclusion of inducible and/or conditional knockout models when available is critical.

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Data availability

No data was used for the research described in the article.

Abbreviations:

ATX	autotaxin

cAMP	adenosine 3′,5’-cyclic monophosphate
DRG	dorsal root ganglion
EMT	epithelial to mesenchymal transition
Enpp2	ectonucleotide pyrophosphatase phosphodiesterase 2
GPAT	glycerol-3 phosphate acyltransferase
GPCR	G protein-coupled receptor
HMC-1	human mast cells
ISC	intestinal stem cells
LPA	lysophosphatidic acid
LPAR	lysophosphatidic acid receptor
MMP	matrix metalloproteinase
NSCLC	non-small-cell lung carcinoma
pCREB	cAMP response element binding protein
PLA_1	phospholipase A_1
PLA_2	phospholipase A_2
PLD	phospholipase D
PPARγ	peroxisome proliferator activated receptor gamma
PSNL	partial sciatic nerve ligation
PTC	papillary thyroid carcinoma
tMCAO	transient middle cerebral artery occlusion
TRPV1	transient receptor potential vanilloid 1

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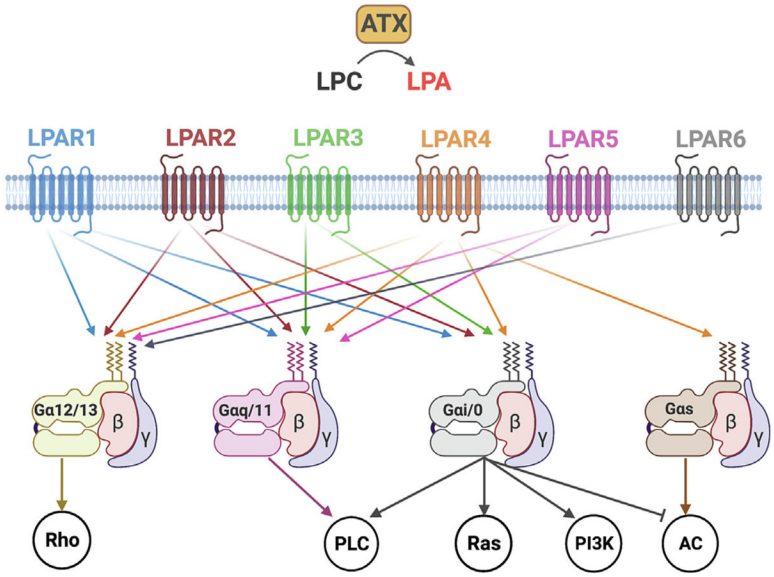

Fig. 1.

LPAR signaling pathway. LPA signaling is mediated through at least six GPCRs (LPAR1–6). LPAR1–6 can couple to different G protein family members ($G\alpha_{12/13}$, $G\alpha_{q/11}$, $G\alpha_{i/0}$, or $G\alpha_{s}$) to activate different downstream pathways, resulting in a variety of cellular responses. The G proteins with which LPAR1 interacts are represented by blue arrows, whereas those interacting with LPAR2, LPAR3, LPAR4, LPAR5 and LPAR6 are indicated by red, green, orange, pink and gray arrows, respectively. Abbreviations: AC, adenylate cyclase; ATX, autotaxin; LPC, lysophosphatidylcholine; PI3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; Ras, rat sarcoma protein; Rho, Ras homolog protein.

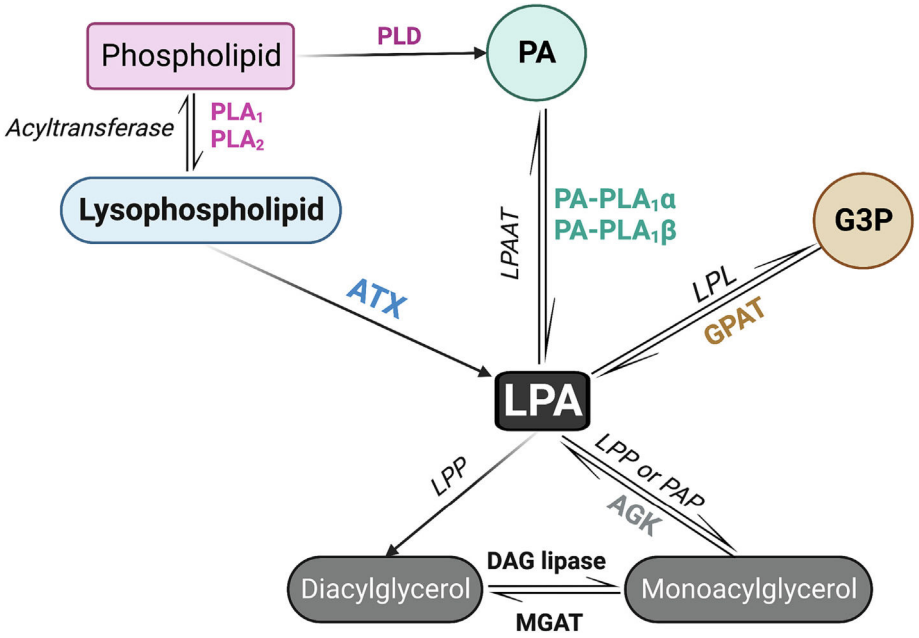

Fig.2.

LPA biosynthesis and degradation pathways. LPA can be synthesized from lysophospholipids, phosphatidic acid (PA), glycerol-3 phosphate, or monoacylglycerol by autotaxin (ATX), PA-selective phospholipase $A_1\alpha$ (PA-$PLA_1\alpha$) or β (PA-$PLA_1\beta$), glycerol-3 phosphate acyltransferase (GPAT), and acylglycerol kinase (AGK), respectively. Conversely, LPA can be converted to PA by LPA acyltransferase (LPAAT), to glycerol-3 phosphate by lysophospholipase (LPL), and to monoacylglycerol by lipid phosphate phosphatase (LPP) or phosphatidate phosphatase (PAP). Abbreviations: G3P, glycerol-3 phosphate; DAG lipase, diacylglycerol lipase; MGAT, monoacylglycerol acyltransferase; PLA_1, phospholipase A_1; PLA_2, phospholipase A_2; PLD, phospholipase D.

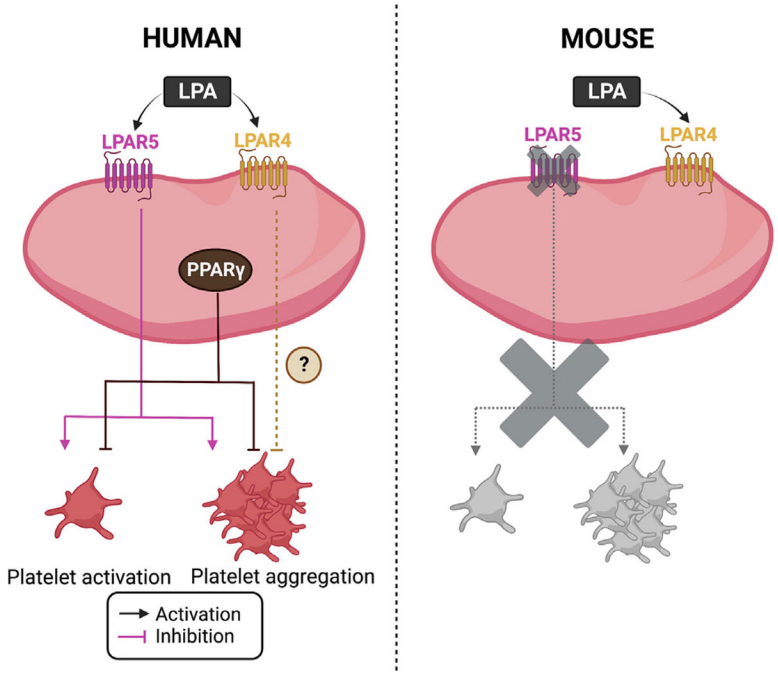

Fig. 3.

Role of LPAR5 in regulating platelet function. LPA induces human platelet activation and aggregation through LPAR5. One study proposed the potential involvement of LPAR4 and PPARγ in inhibiting platelet aggregation as their expression was elevated in platelets that were nonresponsive to LPA stimulation (Pamuklar et al., 2008). While the involvement of PPARγ in inhibiting platelet function has been demonstrated with other PPARγ ligands, more research is needed to confirm the role of LPAR4 in modulating platelet function. Murine platelets express LPAR4 rather than LPAR5, which could explain in part why LPA does not induce platelet activation and aggregation in mice.

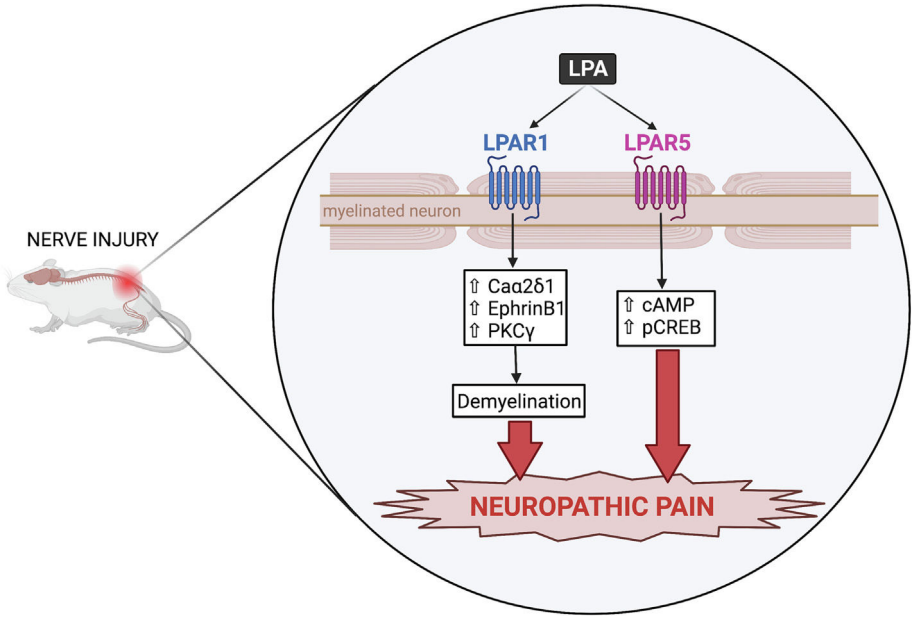

Fig. 4.

Role of LPAR in neuropathic pain. Upon nerve injury, LPA can induce neuropathic pain *via* two pathways. The first involves activation of LPAR1, which upregulates neuropathic pain markers such as calcium channel Caα2δ1, ephrinB1 and PKCγ, resulting in the demyelination of DRG neurons. The second pathway involves activation of LPAR5, which increases phosphorylation of cAMP and pCREB activation.

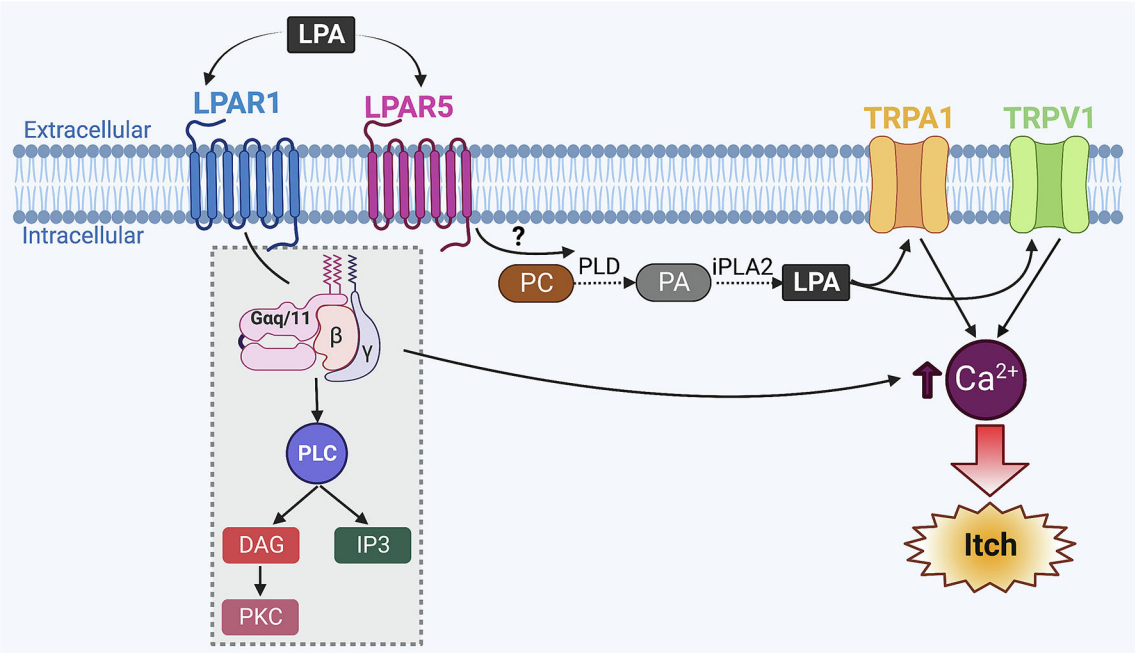

Fig. 5.

Role of LPAR in itch. LPA signaling has been reported to regulate itch sensation *via* activation of LPAR1 and/or LPAR5. However, the downstream signaling pathway(s) linking LPAR1 to itch has not been elucidated (gray box). Although LPAR1 has been shown to activate PKCϵ to potentiate TRPV1 activity leading to pain sensation, whether this pathway is involved in mediating itch sensation remains unknown (Pan et al., 2010). Likewise, activation of LPAR5 has been shown to induce itch *via* PLD-iPLA$_2$ generation of intracellular LPA, which in turns activates TRPA1 and TRPV1. However, experimental evidence linking LPAR5 to direct PLD activation is currently lacking (denoted as question mark).

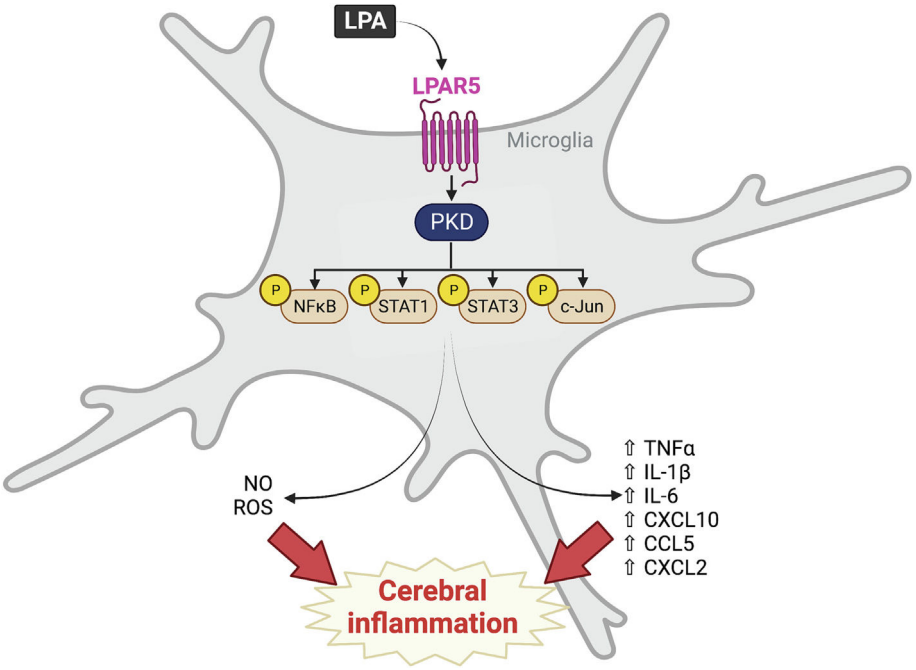

Fig. 6.

Role of LPAR5 in regulating cerebral inflammation. In microglia, LPAR5 activates the protein kinase D pathway, resulting in the phosphorylation of transcription factors such as NFκB, STAT1, STAT3 and c-Jun. This event causes an increase in proinflammatory factors such as TNFα, IL-1β, IL-6, CXCL10, CCL5, CXCL12, nitric oxide (NO) and reactive oxigen species (ROS), all of which cause cerebral inflammation.

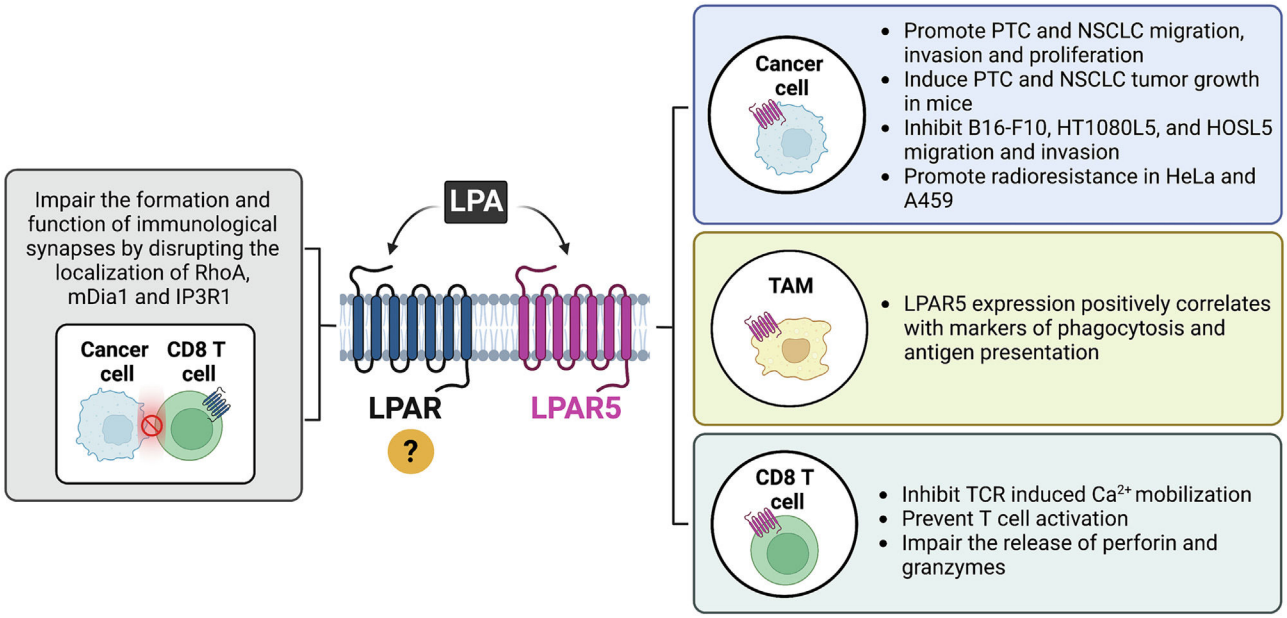

Fig. 7.

Role of LPAR5 in cancer. Depending on the type of cancer, LPAR5 can mediate pro- or anti-tumorigenic functions. In terms of the role of LPAR5 in immune cells, LPAR5 expression on TAM correlates positively with markers of phagocytosis and antigen presentation, whereas LPAR5 expression on CD8 T cells inhibits TCR induced Ca mobilization, T cell activation, and impair the release of perforin and granzymes. Furthermore, LPA signaling impairs the formation and function of immunological synapses in CD8 T cells by altering the localization of RhoA, mDia1, and IP3R1. The question mark indicates that the LPAR responsible for mediating this effect has not been experimentally determined.

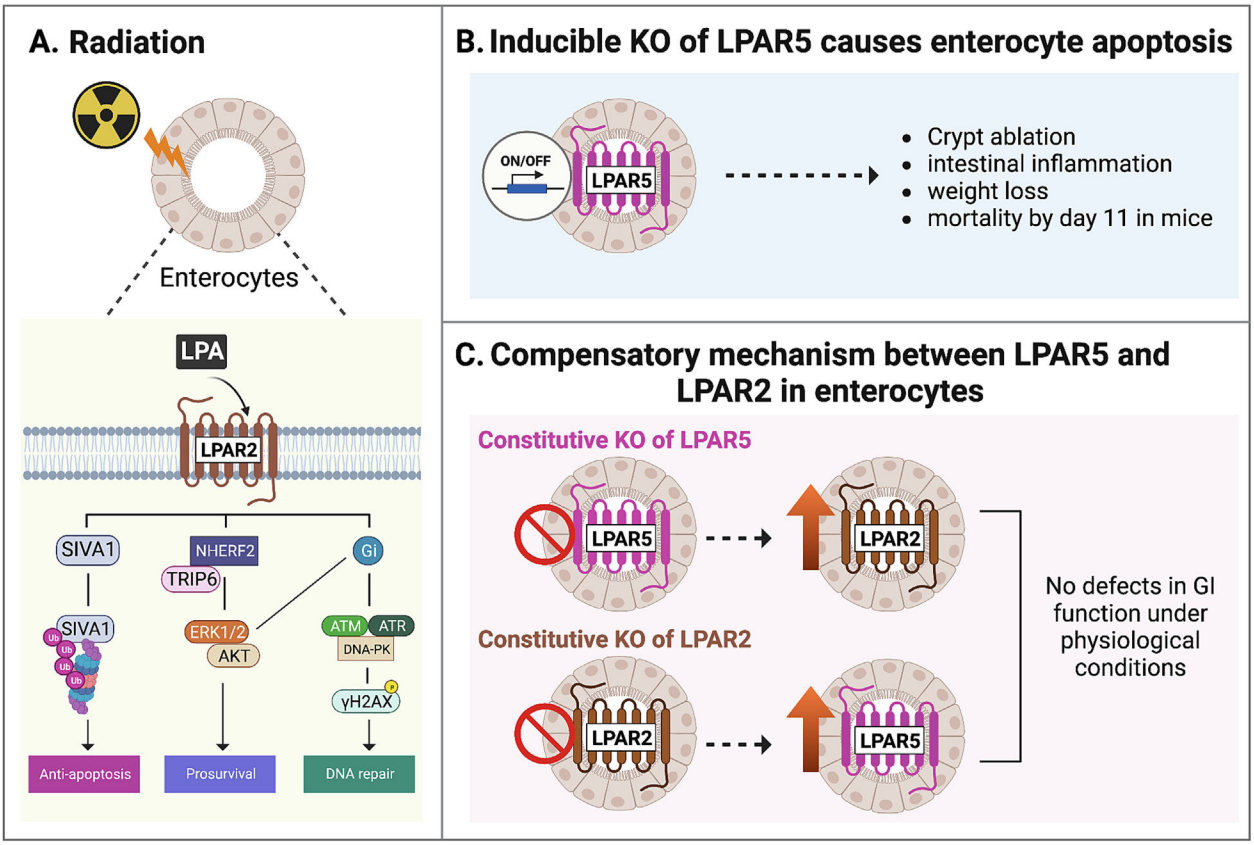

Fig. 8.

Role of LPAR in regulating intestinal epithelium repair and homeostasis. (A) LPAR2 protects enterocytes from radiation-induced apoptosis by promoting the proteasomal degradation of pro-apoptotic SIVA1, activation of ERK1/2 and AKT prosurvival pathways, and repairing DNA damage. Figure adapted from (Tigyi et al., 2019) (B) Although inducible *Lpar5*^{iKO} mice show crypt ablation, intestinal inflammation, weight loss, and mortality by day 11, (C) constitutive *Lpar5*^{cKO} mice show no GI abnormalities under physiological conditions. In the enterocytes of constitutive *Lpar5*^{cKO} mice, a compensatory upregulation of LPAR2 was observed, which was responsible for maintaining normal GI functions in these mice. Similarly, LPAR5 was found to be upregulated in the enterocytes of germline *Lpar2*$^{-/-}$ KO mice in order to maintain normal GI functions under physiological conditions.

Table 1

List of published LPAR5 antagonists. No effect (NE).

Compound	IC_{50} at LPAR5	Selectivity	References
H2L 5987411	3.5 μM [Ca^{2+} assay, RH7777 cells]	NE at LPAR1–3 IC_{50} 1.4 μM at LPAR4 [Ca^{2+} assay]	(Williams et al., 2009)
H2L 5765834	0.46 μM [Ca^{2+} assay RH7777 cells]	NE at LPAR2 and LPAR4 IC_{50} 0.09 μM at LPAR1 [Ca^{2+} assay] IC_{50} 0.75 μM at LPAR3 [Ca^{2+} assay]	(Williams et al., 2009)
TCLPA5–4	0.8 μM [Ca^{2+} assay] 2.2 μM [human platelets]	NE at >80 drug targets	(Kozian et al., 2012)
Cpd3/UA08025	0.14 μM [MCP-1 release, HMC-1 cells] 0.14 μM [Ca^{2+} assay, HMC-1 cells] 0.73 μM [Ca^{2+} assay, BV-2 cells] 3 μM [Ca^{2+} assay, B103 cells] 16.9 μM [β-arrestin assay]	IC_{50} > 10 μM at LPAR1–3 IC_{50} 0.9 μM at LPAR4 [Ca^{2+} assay]	(Kozian et al., 2016; Lee et al., 2020)
AS2717638	0.04 μM [cAMP assay, CHO cells] 0.33 μM [TGFα shedding assay, HEK cells; unpublished]	IC_{50} > 10 μM at LPAR1–3 [Ca^{2+} assay] NE at 10 μM on binding of 22 other targets (receptors/channels)	(Murai et al., 2017)