REVIEW ARTICLE

The Role of Lysophosphatidic Acid in Adult Stem Cells

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Stem cells are undifferentiated multipotent precursor cells that are capable both of perpetuating themselves as stem cells (self-renewal) and of undergoing differentiation into one or more specialized types of cells. And these stem cells have been reported to reside within distinct anatomic locations termed "niches". The long-term goals of stem cell biology range from an understanding of cell-lineage determination and tissue organization to cellular therapeutics for degenerative diseases. Stem cells maintain tissue function throughout an organism's lifespan by replacing differentiated cells. To perform this function, stem cells provide a unique combination of multilineage developmental potential and the capacity to undergo self-renewing divisions. The loss of self-renewal capacity in stem cells underlies certain degenerative diseases and the aging process. This self-renewal regulation must balance the regenerative needs of tissues that persist throughout life. Recent evidence suggests lysophosphatidic acid (LPA) signaling pathway plays an important role in the regulation of a variety of stem cells. In this review, we summarize the evidence linking between LPA and stem cell regulation. The LPA-induced signaling pathway regulates the proliferation and survival of stem cells and progenitors, and thus are likely to play a role in the maintenance of stem cell population in the body. This lipid mediator regulatory system can be a novel potential therapeutics for stem cell maintenance.

Keywords: Stem cells, Lysophosphatidic acid, Pluripotent stem cells, Neural stem cells, Hematopoietic stem cells, Mesenchymal stem cells, Cancer stem cells

Introduction

LPA is a phospholipid that induces a variety of cellular responses in most cell types, including intracellular calcium mobilization, stress fiber formation, cell rounding, neurite retraction, proliferation, cell survival, migration, and differentiation (1-4). The LPA-induced cellular responses occur through activation of their G-coupled LPA receptors, and LPA activates these receptors through heterotrimeric G_α proteins (5, 6). Up to date, six G-coupled LPA receptors (LPA_{1-6}) have been identified, and they have a broad tissue distribution (7). LPA_{1-3} receptors have been shown to mediate their cellular effects through mechanisms involving phospholipase C activation and calcium mobilization (3, 8, 9). Whereas, LPA_1 and LPA_2 receptors can mediate LPA-induced Rho activation required for morphological effects (10-15). LPA canbe produced from lysophosphatidylcholine (LPC) by removal of the choline moiety by the lysophospholipase D (lyso-PLD) (16). LPC is an intermediate in multiple lipid metabolic pathways. These results suggest the distinct signaling mechanisms of
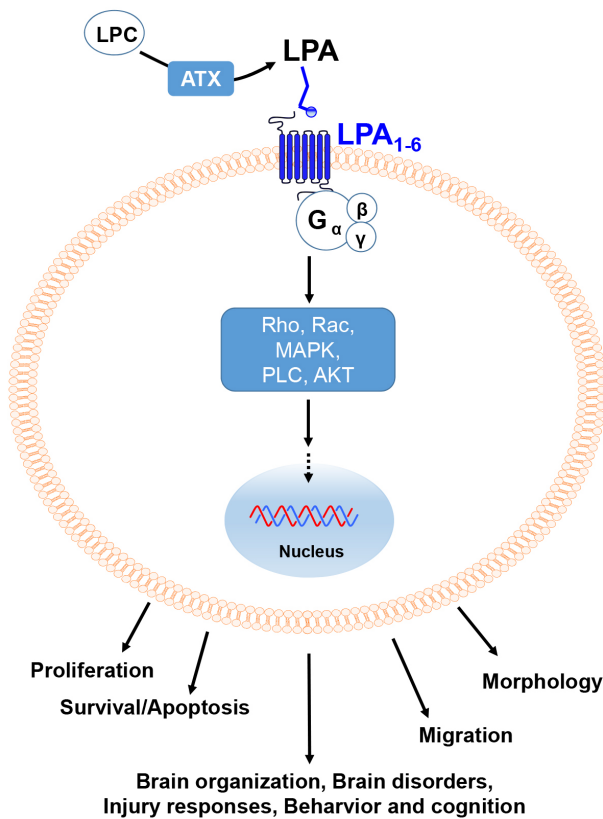
Fig. 1. LPA signaling pathways. LPA activates G-protein-coupled receptors and initiates various downstream signaling cascades. LPA influences subsequent cellular processes such as proliferation, survival, apoptosis, morphological change, and migration, as well as brain organization within the nervous system.

LPA receptors are responsible for the diverse function of LPA in different cell types (Fig. 1).

Role of the LPA in Embryonic Development

During the development, LPA is involved in various biological processes, including brain development (17-19). LPA mediates numerous aspects of progenitor behavior, including proliferation and cell cycle-associated morphological changes in the embryonic cerebral cortex (20, 21). The LPA_1 receptor is abundantly expressed in progenitor cells of the embryonic cerebral cortex (21, 22). LPA_1 receptor knockout (KO) mice were approximately 50% neonatal lethality and result in craniofacial dysmorphism due to defective suckling behavior, and generation of a small fraction of pups with a frontal hematoma (23). However, LPA_2 receptor KO mice displayed no obvious phenotypic abnormalities. $LPA_{1/2}$ receptors double knockout (DKO) mice displayed no additional phenotypic abnormalities relative to LPA_1 receptor KO mice except for an increased

incidence of perinatal frontal hematoma (17). Furthermore, LPA-induced responses, including phospholipase C activation, Ca^{2+} mobilization, adenylyl cyclase activation, proliferation, JNK activation, AKT activation, and stress fiber formation were absent or severely reduced from $LPA_{1/2}$ receptors DKO mouse embryonic fibroblast. Thus, these results supported a role for LPA signaling through the LPA_1 receptor in nervous system development. LPA_3 receptor-deficient female mice showed delayed embryo implantation, altered embryo spacing, and reduced litter size, resulting in the delayedembryonic development and hypertrophic placentas and embryonic death (24). This was attributed to a down-regulationof cyclooxygenase 2 which led to reduced levels of prostaglandins E2 and I2, which are essential players in implantation (17). The LPA_4 receptor was shown to mediate the LPA-induced suppression of cell migration *in vitro* (25). LPA_4 receptorKO embryos died during embryonic development and showed several abnormalities in the blood and lymphatic vascular system (26). LPA_4 receptor deletion caused a potentiation of AKT and Rac activation, implying that the LPA_4 receptor negatively regulates the PI3K pathway, which is in contrast to activation of this pathway by other LPA receptors (27).

LPA in the Regulation of Pluripotent Stem Cells

Embryonic stem cells are derived from the blastocyst stage of early mammalian embryos, are distinguished by their ability to differentiate into any embryonic cell type and by their ability to self-renew. The totipotent cells are the fertilized eggs of mammals and able to generate new individuals (28). Embryonic stem cells are pluripotent, having the ability to generate all body and extra-embryonic tissues. Also, embryonic stem cells have a normal karyotype, maintaininghigh telomerase activity, and exhibit remarkable long-term proliferative potential (29).

In the mouse embryonic stem cells, the LPA_5 receptor has been identified (30, 31), and while the physiological relevance of LPA in mouse embryonic stem cells has not been established, LPA is known to stimulate the phosphorylation of ERK and JNK and result in the *c-Fos* induction (32). In the human embryonic stem cells, LPA_{1-3} receptors have been identified (33, 34), and LPA maintains undifferentiated human embryonic stem cell lines in the presence of mouse embryonic fibroblasts (33). These human embryonic stem cells retain functional gap junctions (35).

Induced pluripotent stem cells are pluripotent stem cells that can be reprogramed directly from somatic cells by introducing four specific genes (*c-Myc*, *Oct3/4*, *Sox2*, and *Klf4*) (36). Recent studies demonstrate that LPA modulates the

Hippo pathway in both human embryonic stem cells and human-induced pluripotent stem cells by activating YAP/TAZ (37, 38). These data suggest that differential LPA receptors affect pluripotent stem cell maintenance.

LPA in the Regulation of Neural Stem Cells

Neural stem cells are self-renewing, multipotent cells that firstly generate the radial glial progenitor cells that generate the neurons and glia of the nervous system of all animals during embryonic development (39). These neural stem cells are located in the subventricular zone and the spinal cord (40). These stem cells can give rise to either neural or neuronal progenitor cells and are involved in the neurogenesis of the central nervous system.

A recent study has been reported that neural stem cells migrate to the sites of injury for the repair of damaged tissue (41). LPA signaling influences several developmental processes within the nervous system (18). LPA$_{1-3}$ receptors are expressed in neural stem cells (42). LPA is found in the embryonic brain, neural tube, choroid plexus, meninges, blood vessels, spinal cord and cerebrospinal fluid (5), and regulates morphological rearrangements, proliferation, and differentiation of neural stem cells (21, 23, 43, 44). Neural stem cells can be maintained in culture as neurospheres by the presence of basic fibroblast growth factor and epidermal growth factor (45, 46). LPA inhibited the basic fibroblast growth factor-induced growth of neurospheres from cortical neural stem cells (47). In contrast, LPA has been shown to induce neurosphere formation

from mouse forebrain neural stem cells (42). In rat cortical neural stem and progenitor cells, while LPA stimulates neuronal differentiation and migration, low concentrations of LPA induce proliferation (48). Besides, it has been reported that LPA does not induce proliferation but affects morphological rearrangements in rat hippocampal neural stem and progenitor cells (49-51).

LPA stimulates neuronal differentiation of cortical neuroblasts, neural progenitors, and early cortical neurons via the LPA$_1$ receptor (44, 47). LPA is an essential factor for cortical neurogenesis (52) that induces the depolarization of mouse cortical neuroblasts and activates the electrical responses in neuroblasts via GABA signaling (53). Oligodendrocyte progenitors share properties with both stem cells and progenitor cells and give rise to oligodendrocytes which is responsible for neuron myelination within the central nervous system (54, 55). LPA$_1$ receptor on oligodendrocyte progenitors has only been examined in rodents and inducesthe retraction of processes of oligodendrocyte progenitors (56, 57). Further, LPA was shown to induce cell proliferation in cultured astrocytes, which express *Lpa1*, *Lpa2*, and *Lpa3* genes (58, 59). Also, LPA stimulates astrocyte proliferation through the LPA$_1$ receptor (60). LPA$_1$ receptor gene expression may be induced by LPA stimulation in astrocytes *in vivo*. Together, these studies suggest differential roles of LPA in the biology of neural stem cells and their progenitors (Fig. 2).
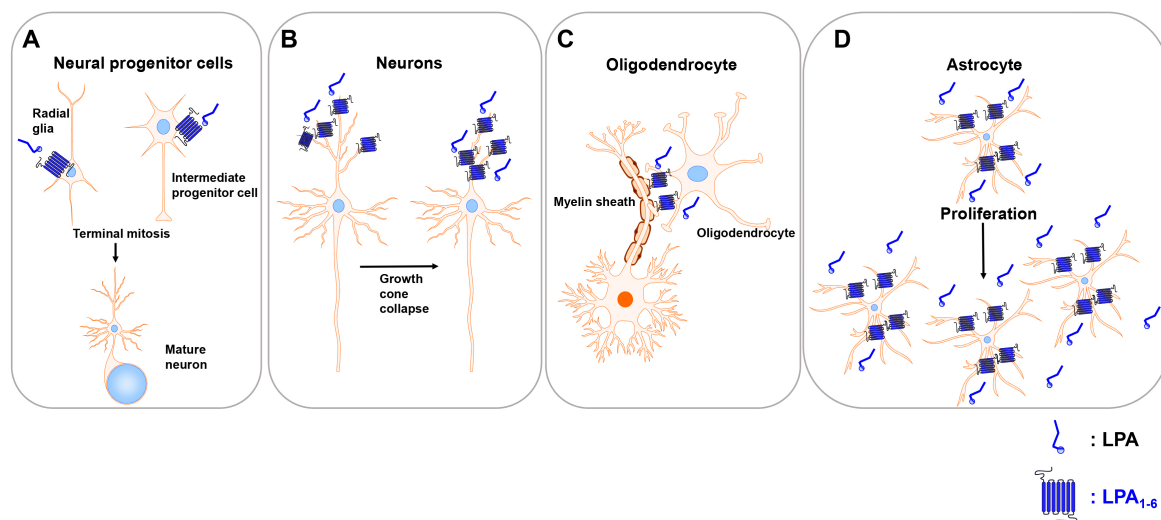

Fig. 2. LPA in the nervous system. (A) In neural progenitor cells, LPA promotes the survival of neural progenitor cells, as well as an increase in terminal mitosis. (B) In neurons, LPA changes to cell morphology and promotes growth cone collapse. (C) In oligodendrocytes, LPA promotes maturation and myelination. (D) In astrocytes, LPA activates the proliferation of astrocytes.

LPA in the Regulation of Hematopoietic Stem Cells

Hematopoietic stem cells mainly reside in the microenvironments of the bone marrow, where they pass through multiple developmental steps to produce mature blood cells (61, 62). Hematopoietic stem cells give rise to different types of blood cells, in lines called myeloid and lymphoid (62). Myeloid cells include monocytes, macrophages, neutrophils, basophils, eosinophils, erythrocytes, and megakaryocytes to platelets. Lymphoid cells include T cells, B cells, natural killer cells, and innate lymphoid cells.

LPA induced migration of c-Kit$^+$ cell and enhanced the chemotactic migratory response of the primitive hematopoietic stem cells to stromal-derived factor 1 through a mechanism involving the activation of the Rac, Rho, and Cdc42 proteins (63). LPA decreased the adhesion of the myeloid progenitor cell line TF1 through a Rho-dependent pathway (64). LPA facilitates the migration of CD34$^+$ hematopoietic progenitor cells (65) and triggers an invasion of hematopoietic stem cells to the stromal cell layer (66). Furthermore, LPA participates in EPO-dependent erythropoiesis by activating the LPA$_3$ receptor (67). Also, in vitro stimulation of CD34$^+$ human hematopoietic progenitors by LPA induced myeloid differentiation but did not affect lymphoid differentiation (68).

LPA receptors were expressed at significantly higher levels on common myeloid progenitors than common lymphoid progenitors suggesting that LPA acts on lineage specification (68). Especially, LPA$_1$ and LPA$_2$ receptors are expressed in Lin$^-$Sca1$^+$c-Kit$^+$ hematopoietic stem and progenitor cells (63). In contrast, the less primitive cKit$^-$ cells expressed the LPA$_2$ receptor, but not the LPA$_1$ receptor. Also, the LPA$_1$ receptor has important roles in the regulation of migration in hematopoietic stem cells (65). The pharmacological and genetic blockage of the LPA$_1$ receptor inhibited hematopoietic differentiation of mouse embryonic stem cells and impaired the formation of hemangioblasts (69). In K562 human erythroleukemia cells, knockdown of LPA$_2$ receptor enhanced erythropoiesis, whereas knockdown of LPA$_3$ receptor inhibited RBC differentiation (70). The pharmacological activation of LPA receptors can be novel strategies for augmenting or inhibiting erythropoiesis and/or hematopoiesis.

LPA in the Regulation of Mesenchymal Stem Cells

Mesenchymal stem cells are multipotent stromal cells that can differentiate into a variety of cell types, including osteoblasts, chondrocytes, myocytes, and adipocytes (71, 72).

These mesenchymal stem cells play an important role in hematopoietic stem cell differentiation into mature blood cells (73-75). Moreover, bone marrow stromal cells can differentiate into adipose, tendon, cartilage, and bone (76, 77).

LPA$_{1-3}$ receptors have been identified in bone marrow mesenchymal stem cells, and LPA influenced the survival of mesenchymal stem cells (40, 78). LPA increased mesenchymal stem cells survival through ERK1/2 and PI3K/AKT signaling pathway and inhibitshypoxia/serum deprivation-induced apoptosis in mesenchymal stem cells. LPA also inhibited caspase12 pathways via inhibition of p38 signaling in mesenchymal stem cells, and it is involved in LPA$_1$ and LPA$_3$ receptors-linked ERK1/2 pathway (79). This study suggests LPA as a new anti-apoptotic target of mesenchymal stem cells for the therapeuticpotential of cardiac repair. Further, LPA stimulated the migration of bone marrow stromal cells via a Rho-dependent mechanism (80, 81). LPA stimulated VEGF secretion in mesenchymal stem cells but not in cardiomyocytes or cardiac fibroblasts via LPA$_1$ and LPA$_3$ receptors (82). Also, LPA promoted osteogenic differentiation in human mesenchymal stem cells via LPA$_1$ and LPA$_4$ receptors (83). These results suggest a potential role of LPA in the regulation of self-renewal and differentiation of mesenchymal stem cells.

LPA in the Regulation of Hepatic Stem Cells

Oval cells, also known as hepatic stem cells, are reportedly involved in the regeneration of the liver following injury (84), whereas relatively little is known about their response to LPA. During chronic liver injury, oval stem cell proliferation is associated with the up-regulation of the expression of the LPA$_{1-3}$ receptors (85). Taken together, these results suggest that LPA plays critical roles during liver regeneration.

LPA in the Regulation of Cancer Stem Cells

Cancer stem cells were first identified by Bonnet and Dick in acute myeloid leukemia in 1997 (86). Cancer stem cells are cancer cells that have self-renewal capacity and show tumorigenic potential (87-89). These cancer stem cells are hypothesized to persist in tumors as a distinct population and cause relapse and metastasis (90). Cancer stem cells have implications for cancer therapy, including for disease identification, selective drug targets, prevention of metastasis. Thus, the development of targeted therapies can improve the survival and quality of life of cancer patients, especially for patients with metastatic

disease.

Elevated LPA levels have been detected in the ascites of 98% of ovarian cancer patients (27). LPA treatment stimulates the expression of *OCT4*, *SOX2*, and *ALDH1* genes which are cancer stem cell-associated, and drug transporters in ovarian cancer stem cells (91). In ovarian cancer stem cells, LPA was found to upregulate the expression of hypoxia-inducible factor-1-alpha, which plays a central role in tumor angiogenesis (92), whereas this was inhibited by the knockdown of LPA_2 or LPA_3 receptors (93). These results show that LPA is implicated in tumor angiogenesis.

Moreover, LPA promoted cancer stem cell-like characteristics, such as sphere-forming ability, resistance to anti-cancer drugs, and tumorigenic potential in xenograft transplantation (91). Knockdown or pharmacological inhibition of the LPA_1 receptor reduced the LPA-stimulated proliferation and acquisition of cancer stem cell-like properties in ovarian cancer cells (88). These results suggest that LPA plays a key role in the self-renewal, therapeutic resistance, and metastasis of ovarian cancer stem cells.

LPA in the Regulation of Adult Somatic Cells

LPA is also implicated in vasculardevelopment and endothelial cell development, such as vasculogenesis, angiogenesis, and vascular maturation during the development. The first study that linked LPA to vascular development was that of the Autotaxin KO mice during the development (94). Autotaxin, a member of the ectonucleotide pyrophosphate and phosphatase family, primarily catalyzes the hydrolysis of lysophosphatidylcholine, resulting in LPA production (7, 95). *Autotaxin*-deficient mice die at E9.5 with profound vascular defects in the yolk sac and embryo, and neural tube malformations. $LPA_{1/2}$ receptors DKO mice also showed blood within the lateral ventricles during the development. LPA was observed to facilitate the closure of wounded endothelial cells *in vitro*. This was due to a stimulation of both endothelial cell migration and proliferation by LPA treatment (96). Also, LPA modulates circulating monocyte migration via LPA-stimulated endothelial cells (97).

LPA has also been implicated in the regulation of pathophysiologic vascular responses in the endothelial and vascular smooth muscle cells. LPA was found to signal through $G_{\alpha q}$ to promote the growth and migration of vascular smooth muscle cells (98). Mice deficient in LPA_1 and LPA_2 receptors were protected from intimal hyperplasia (99) that induce migration of smooth muscle cells. LPA promoted human platelet development by inducing plate-

let shape change and calcium mobilization (27). LPA also induced the aggregation of platelets, which is essential in thrombosis (100). LPA is involved in vascular injury by causing endothelial cell death and vascular degeneration (101, 102). Loss of confluence and vascular integrity of endothelial cells was observed in vivo when exposed to LPA. Collectively, recent studies indicate that LPA signaling plays a role in the development of the vasculature and endothelial cells.

Liver sinusoidal endothelial cells constitute the innermost layer of hepatic blood vessels (103), and thus, directly encounter circulating erythrocytes and immune cells and provide a physical barrier for underlying hepatocytes (104). LSECs contribute to the maintenance of liver homeostasis and participate in metabolite transportation, immune regulation, and the development or resolution of pathological conditions, such asinflammation, cirrhosis, hepatocellular carcinoma, and liver regeneration (105, 106). LPA_1 and LPA_3 receptors are expressed in mouse liver sinusoidal endothelial cells (107). LPA has potent effects on cell migration (96) and membrane permeability in liver sinusoidal endothelial cell membranes (108).

In the immune cells, LPA enhances the motility of human and mouse T cells *in vitro* (109-111), induces human natural killer cell chemotaxis (112), accelerates the development of human mast cells (113), influences Neutrophils (114-116), Macrophages (117), and B cells (118). Also, LPA induces chemotaxis of immature mouse bone marrow-derived Dendritic cells (119).

These results suggest that LPA plays a key role in lymphocyte homing and inflammation.

Conclusions

Remarkable progress has been made in the last decade in understanding the role of LPA in the regulation of stem cells. This has been driven largely by the discovery of G protein-coupled receptors for LPA and also by the characterization of many of the enzymes involved in lysophospholipid metabolism. LPA controlsthe reproductive, gastrointestinal, vascular, nervous, and immune systems (120), and it plays an important role in the regulation of stem cells and their progenitors (121). LPA also appears to regulate the proliferation, survival, mobilization, migration, and differentiation of the stem cells. Thus, it is likely that LPA plays a role in the maintenance of stem cell populations in the body. Collectively, the modulation of LPA-mediated signaling pathways may provide opportunities for future therapeutics by regulating the self-renewal and differentiation of stem cells.

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Potential Conflict of Interest

The authors have no conflicting financial interest.

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