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Review article

The role of lysophosphatidic acid in the physiology and pathology of the skin

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ABSTRACT

Lysophosphatidic acid (LPA) is the simplest phospholipid found in nature. LPA is mainly biosynthesized in tissues and cells by autotoxin and PA-PLA1α/PA-PLA1β and is degraded by lipid phosphate phosphatases (LPPs). It is an important component of biofilm, an extracellular signal transmitter and intracellular second messenger. After targeting to endothelial differentiation gene (Edg) family LPA receptors (LPA1, LPA2, LPA3) and non-Edg family LPA receptors (LPA4, LPA5, LPA6), LPA mediates physiological and pathological processes such as embryonic development, angiogenesis, tumor progression, fibrogenesis, wound healing, ischemia/reperfusion injury, and inflammatory reactions. These processes are induced through signaling pathways including mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K)/Akt, protein kinase C (PKC)-GSK3β-β-catenin, Rho, Stat, and hypoxia-inducible factor 1-alpha (HIF-1α). LPA is involved in multiple physiological and pathological processes in the skin. It not only regulates skin function but also plays an important role in hair follicle development, skin wound healing, pruritus, skin tumors, and scleroderma. Pharmacological inhibition of LPA synthesis or antagonization of LPA receptors is a new strategy for the treatment of various skin disorders. This review focuses on the current understanding of the pathophysiologic role of LPA in the skin.

1. Introduction of LPA

Lysophosphatidic acid (LPA), the simplest phospholipid found in nature, is a key precursor in the early stage of cellular phospholipid biosynthesis [1,2]. It is an important component of biofilm, an extracellular signal transmitter and an intracellular second messenger. It exerts a wide range of biological functions by binding to specific receptors on target cells [3,4]. LPA is composed of a glycerol backbone with a hydroxyl group, a phosphate group, and a long fatty acyl chain [3,4]. LPA is water soluble, particularly in solutions without calcium or magnesium ions [5,6]. The length of the fatty acyl chain is closely associated with the biological effects of LPA. LPA with a shorter fatty acyl chain is less biologically active. LPA exhibits the greatest biological activity when its fatty acyl chain length is in the range of C16–C20 [7,8].

2. LPA metabolism

LPA is present in large quantities in plasma but is also present in other biological fluids, such as skin blisters, ascites, tears, follicular fluid, saliva, extracellular fluid, and arthritis fluid [1]. In biological fluid, LPA binds to several proteins, including albumin and gelsolin, which protect LPA from phospholipase digestion and maintain its stability and impermeability [9–12]. LPA is mainly produced by thrombin-stimulated platelets. It is also generated by injured cells or cells such as fibroblasts, adipocytes, nerve cells, and tumor cells after stimulation with cytokines or growth factors [1,13,14]. Several mechanisms have been clearly established to generate LPA [15–18]. LPA was found to be mainly synthesized through both extracellular and intracellular mechanisms from membrane phospholipids [19]. The secreted lysophospholipase D enzyme called autotaxin, which converts lysophosphatidylcholine into LPA, is mainly responsible for extracellular biosynthesis of LPA [20,21]. At the same time, LPA is also synthesized intracellularly in the endoplasmic reticulum and mitochondrial membrane by three major enzymes including glycerophosphate acyltransferase, acylglycerol kinase, and phospholipase A [19,22,23]. For example, glycerophosphate acyltransferases esterify long-chain fatty acyl-coenzyme As (CoAs) such as C16:0, C18:0, C18:1 fatty acyl CoAs to

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glycerol-3-phosphate to generate various molecular species of LPA [16,24,25]. Acylglycerol kinase is a lipid kinase that phosphorylates monoacylglycerol to LPA [23]. The phosphatidic acid (PA)-selective phospholipases A1α (PA-PLA1α) and PA-PLA1β can hydrolyze PA to generate LPA [26]. LPA is mainly degraded by lipid phosphate phosphatases (LPPs) [27]. LPPs include the LPP1, LPP2, and LPP3 subtypes [27]. There is evidence that downregulation of LPPs in tumor cells is one of the mechanisms underlying an increase in the LPA level [28]. The mechanisms and regulatory networks of the generation and degradation of LPA are still not fully explained. More in-depth studies are required.

3. Physiological and pathological effects of LPA and its regulatory mechanism

Since the 1960s, LPA has been reported to promote smooth muscle contraction, induce platelet aggregation, and affect blood pressure and other physiological functions in the intestine, airway, uterus, and blood vessels [29–33]. Recent studies have found that LPA can be used as an intracellular messenger to mediate many physiological and pathological processes including embryonic development, angiogenesis, tumor progression, fibrogenesis, wound healing, ischemia/reperfusion injury, and inflammation, which occurs by the activation intracellular signaling pathways through G-protein coupled receptors, thereby regulating cell proliferation, contraction, migration, differentiation, and survival [3,34–36].

LPA exhibits multiple biological functions mainly through its receptors. LPA receptors are divided into the endothelial differentiation gene (Edg) family (LPA1, LPA2, LPA3) and the non-Edg family [37,38]. Edg family members have recently been found to be widely expressed in a variety of tissues, but the expression of non-Edg family members is low in many tissues [39]. LPA likely produces different physiological signals after binding to different receptors [40]. There is evidence that LPA promotes the fibrosis of many organs such as the skin, lung, kidney, and peritoneum through its receptor LPA1 and then accelerates the healing of skin wounds [1]. LPA reportedly promotes angiogenesis through its receptors LPA1, LPA2, and LPA3 [13]. Jongsma et al. [41] found that LPA inhibits the migration of B16F10 melanoma cells through its receptor LPA5. Previous studies have reported that LPA regulates hair follicle morphogenesis through its receptor LPA6 [15,42].

After binding to its receptors, LPA exerts its biological functions through signaling pathways, including mitogen-activated protein kinase (MAPK), signal transducers and activators of transcription (STAT), Wnt, Rho, nuclear factor-kappaB (NF-κB), and hypoxia-inducible factor-1alpha (HIF-1α) (Fig. 1). LPA activates JNK/MAPK through PI3K- and Rac1-dependent pathways and p38/MAPK through PI3K- and Cdc42-dependent pathways to promote cell migration [43]. It can also activate the ERK/MAPK signaling pathway to promote DNA synthesis in fibroblasts [44,45]. LPA activates the Jak-STAT signaling pathway to induce the expression of transcription factors including STAT3, NF-κB, and ATF-2, which subsequently induces the production of inflammatory cytokines, chemotactic factors, and COX-2, thus mediating an inflammatory reaction [46–50]. LPA activates and aggregates β1 integrin and then promotes epithelial-mesenchymal transition in ovarian cancer cells by activating the β-catenin-dependent Wnt signaling pathway [51]. LPA activates RhoA through the NF-κB/IκBα signaling pathway, which activates RhoA kinase (ROCK) to mediate reconstruction of the cytoskeleton and to maintain cellular morphology [52–54]. LPA can also activate the Rho/ROCK pathway, increase Wnt10b expression, activate β-catenin, and then enhance the Wnt/β-catenin signaling pathway-mediated anti-adipogenic action [55]. In addition, LPA can activate the NF-κB signaling pathway through the Rho/ROCK pathway to promote the invasion of tumor cells [56]. After binding to its receptors, LPA activates Gαi2 first and then Src, and Src-dependent signaling upregulates HIF-1α [57]. LPA is involved in the regulation of epithelial-mesenchymal transition, angiogenesis, and cell proliferation by altering HIF-1α expression [57–59].

LPA exerts biological functions through multiple signaling pathways in addition to G protein-coupled receptors. For example, LPA can cause Cl^- efflux from fibroblasts, leading to depolarization of the cell membrane and production of a bioelectrical signal [60]. LPA inhibits gap-junctional communication between cells [61]. Taken together, LPA is responsible not only for signal transduction through its receptors but also exerts biological functions through LPA receptor-independent pathways. However, the mechanisms underlying LPA-mediated intracellular and intercellular signal transduction remain poorly understood. In addition, LPA receptor inhibitors can antagonize the LPA signaling pathway, which plays a role in the regulation of physiological and pathological processes in the skin.

It is noteworthy that LPA exhibits biological functions not only through receptors on the cell surface but also via intracellular nuclear hormone receptors, such as PPARγ, which functions as a lipid-activated transcription factor [62,63]. For example, LPA has been reported to promote neurite outgrowth/proliferation, macrophage development and human CD34(+) cell survival through the PPARγ pathway [64–66].

4. The biological role of LPA in the skin

4.1. LPA and skin function

LPA participates in the regulation of skin protection, sensation, and metabolism through a variety of pathways (Fig. 2). In photoaged skin, matrix metalloproteinase-1 (MMP-1) levels are increased and collagen is degraded [67], but LPA can antagonize these changes [68] and thereby inhibit photoaging. An increase in LPA levels in the skin likely worsens inflammatory pain [69]. LPA activates LPA1 followed by the PI3K, ERK, and CREB signaling pathways to induce the expression of hyaluronic acid synthetase 2 (HAS2) and promotes the synthesis of hyaluronic acid in skin fibroblasts, which maintains the skin barrier [70]. LPA can promote the intracellular transfer of calcium ions by stimulating calcium ion channels, which further increases the expression of the skin barrier-related proteins SPT and profilaggrin and contributes to the regulation of skin moisture [71]. LPA can also regulate melanin metabolism; it can downregulate melanin levels through inhibiting microphthalmia-associated transcription factor expression and by decreasing tyrosinase activity [72].

Insight into the structure-activity relationship will help to clarify further functions and mechanisms of LPA in skin physiopathology. Van Corven et al. explored the relationship between LPA with various acyl chains (C18:l, C16:0, C14:0, C12:0, and C10:0) and its mitogenic activity in skin fibroblasts. They found that long-chain LPA (C18:l and C16:0) were by far the most potent in inducing DNA synthesis and that short-chain LPA (C10:0) was almost completely devoid of biological activity [73]. Jalink et al. found that a decrease in chain length of LPA could decrease Ca^{2+} mobilization in epidermoid carcinoma cells [74]. In sum, LPA with longer acyl chains correlate with greater activity in vivo; short acyl chains render the LPA almost inactive [75]. However, more studies are needed to determine how the molecular species of LPA (such as C16:0, C18:0, C18:1, C20:4, C22:5 and C22:6) may play roles in various skin pathologies.

4.2. LPA and hair follicle development

The hair follicle is one of the most unique and complex mammalian micro-organs [76]. Their development is regulated by numerous signaling molecules such as epidermal growth factor receptor (EGFR) and TGF-β [77,78]. The "wavy" hair phenotype likely results from a lack of EGFR and TGF-α [79–82]. LPA and other lipid substances are also involved in the regulation of hair follicle morphogenesis. A previous study has demonstrated that LPA synthases (such as PA-PLA_1α) and

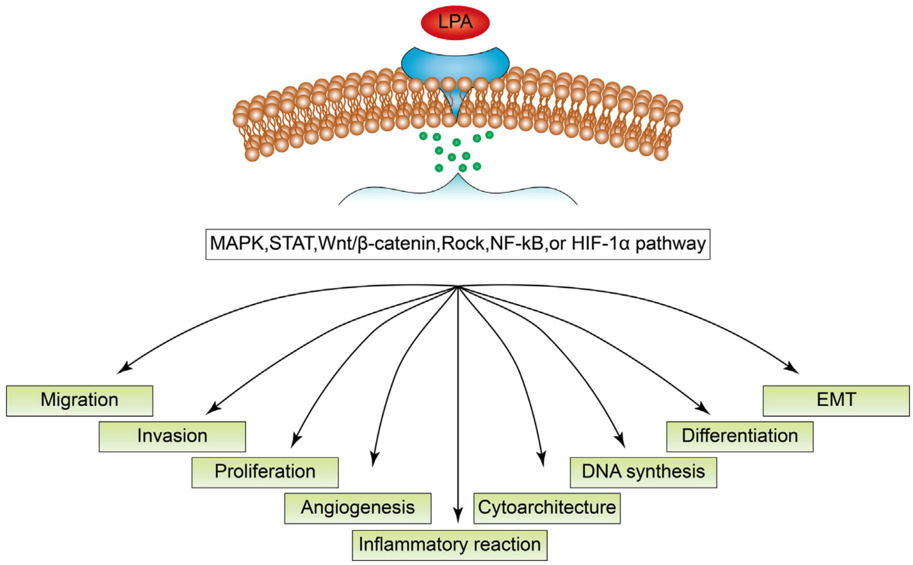

Fig. 1. Multiple biological roles of LPA. LPA exerts biological functions through signaling pathways including MAPK, STAT, Wnt/β-catenin, Rock, NF-κB, and HIF-1α pathway.

LPA receptors are highly expressed in embryonic hair follicles [83]. PA-PLA$_1\alpha$ can convert PA to LPA [79]. After binding to LPA6, LPA participates in the regulation of hair follicle morphogenesis through the TACE-TGFα-EGFR signaling pathway [15,42]. PA-PLA$_1\alpha$ variations lead to congenital hair loss and limited hair growth [84]. Variation in the *LPAR6* gene that encodes LPA6 results in Woolly hair syndrome [85], possibly because of the abnormal aggregation of PA-PLA A1α and LPA6 in the root sheath [79,86]. Fujimoto et al. [79] found that the activation of EGFR through the PA-PLA1α/LPA/LPA6 signaling pathway can regulate the expression of Keratin K71 (KRT71). Keratin is the major structural component of hair follicles and plays a very important role in the formation of keratin intermediate filaments [87,88]. The mutation or abnormal expression of KRT71 results in disrupted keratin filaments and affects hair follicle maturation [79].

4.3. LPA and skin wound healing

Skin wound healing refers to the healing process of skin tissue from a circumscribed injury caused by an external force [89]. The process is manifested as a synergy of various processes including epidermal cell proliferation, extracellular matrix deposition, and wound contraction and reconstruction [90]. LPA has been confirmed to promote the healing of skin wounds from several perspectives. Increased activated platelets and autotoxin in the injured tissue induce the local tissue to produce sufficient LPA to exert biological function [91]. After skin injury, LPA levels in the local skin tissue increase. LPA has also been shown to significantly increase in bullous skin lesions [1]. In vitro experiments have confirmed that LPA can promote the proliferation, differentiation, and migration of keratinocytes and fibroblasts and can participate in skin tissue repair and reconstruction [1,92,93]. Rhim et al. [36] found that LPA can also promote the proliferation of aging fibroblasts. Strong evidence exists that LPA can shorten the wound healing time in animal models of skin wounds [36,94,95], which further confirms LPA's role in wound healing.

The mechanism by which LPA promotes wound healing is likely related to the following: (1) LPA activates Rho GTPase and other signaling pathways or upregulates the expression of laminin-5 and other migration-related proteins to promote the migration of keratinocytes and fibroblasts [36,93,96]; (2) LPA induces epidermal cells to secrete TGF-α, TGF-β and other proteins to promote cell proliferation and differentiation [1]; (3) LPA induces the accumulation of macrophages, leukocytes and other inflammatory cells around the wounds [91]; (4) LPA induces the contraction of fibroblasts and collagen matrix and promotes wound contraction [97,98]; (5) LPA induces the expression of matrix metalloproteinases and participates in the remodeling of extracellular matrix [99]; (6) LPA promotes collagen deposition and matrix thickening [100]; and (7) LPA inhibits the function of TGF-β by activating the ERK signaling pathway, resulting in the reduction of collagen formation and thus, LPA likely plays a role in antagonizing pathological scar proliferation [91,101]. It is noteworthy that the effect of LPA on wound healing is closely related to the concentration of LPA. A low concentration of LPA can promote skin cell proliferation, but LPA at high concentrations has the opposite effect [95].

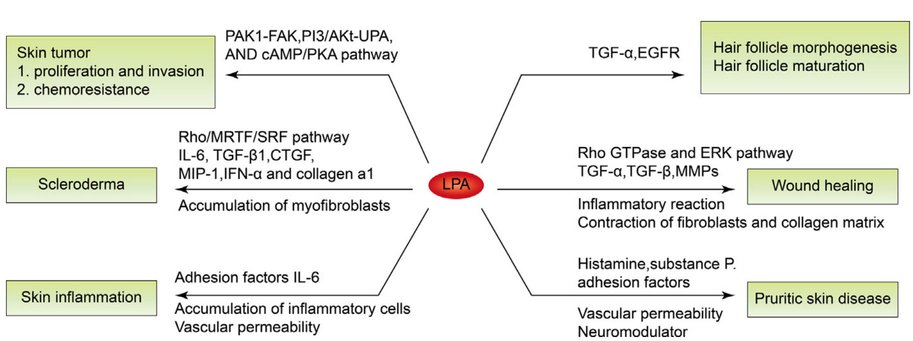

Fig. 2. The role of LPA in skin. LPA plays critical roles in hair follicle development, wound healing, pruritic skin disease, skin tumor, scleroderma, and skin inflammation reaction.

4.4. LPA and pruritic skin disease

Pruritic skin disease is the most common skin disease, manifesting as varying degrees of itching, accompanied by papules, erythema, wheals and other skin lesions [102]. Pruritus is divided into skin-derived pruritus, neurogenic pruritus, neuropathic pruritus, and cardiac pruritus [103,104]. LPA has been found to be associated with both skin-derived and neurogenic pruritus. Intradermal injection of LPA into mice can cause itchiness and scratching [105–107]. LPA can induce mast cells and cutaneous debris to release histamine [108]. H1 histamine receptor antagonists not only inhibit LPA-induced airway hyperresponsiveness but also antagonize LPA-induced pruritic symptoms [105,109]. Intradermal injection of LPA can also induce the release of substance P in the peripheral nerve terminals of mice [110]. These findings suggest that LPA can promote the occurrence of pruritic skin disease through the induction of the release of histamine, substance P, and other pruritic substances. Several studies [107,111] have reported that, in mouse models of atopic dermatitis, serum levels of LPA were significantly increased. Increased LPA may lead to an increase in vascular permeability, induce plasma penetration, and upregulate the expression of adhesion factors, thereby driving immune cells to migrate to the lesion [107,111]. Immune cells in the lesion may release factors such as lysophospholipids that are converted to LPA under the action of autotaxin to initiate or exacerbate the pruritic response [107]. LPA may also be a neuromodulator that can induce pruritus through the opioid receptor system [107]. In patients with cholestasis, serum LPA levels were markedly increased. Pruritic symptoms in patients with cholestasis were closely related to the endogenous opioid peptide. Therefore, LPA possibly mediates the occurrence of pruritic skin disease through the opioid receptor system [106].

4.5. LPA and skin tumor

LPA is involved in the regulation of the occurrence and development of a variety of cancers including liver, rectal, and ovarian cancers [112–114]. LPA also participates in the progression of skin tumors. LPA activates the PAK1-FAK and PI3/Akt-UPA signaling pathways via its receptors to induce the proliferation and invasion of melanoma [17,115]. Studies have found that melanoma cells can adjust intracellular and extracellular LPA concentrations, leading to lower intracellular LPA concentrations and higher extracellular LPA concentrations. The intracellular and extracellular LPA concentration difference drives melanoma cells into the surrounding tissue and vessels [116]; however, the mechanism by which melanoma cells regulate the intracellular and extracellular LPA concentration difference remains unclear. LPA can also decrease the sensitivity of melanoma cells to the chemotherapeutic agent, Paclitaxel [117], which is likely one of the mechanisms of chemoresistance in melanoma cells. Inhibition of autotoxin expression or inhibition of LPA receptors can antagonize LPA-induced melanoma progression [118–120]. Inhibiting LPA production or antagonizing LPA receptors is likely to have clinical benefits, by inhibiting melanoma progression or increasing chemosensitivity. It is noteworthy that LPA can activate the cAMP/PKA signaling pathway through the LPA5 receptor to inhibit the migration of B16F10 melanoma cells. In addition, LPA can promote cell proliferation and migration in head and neck squamous cell carcinoma [38]. LPA binds to Edg receptors to activate intracellular signaling pathways via Gi, Gq and G12/13 proteins and induces the malignant behavior of tumor cells [121,122]. Moreover, the binding of LPA to Edg receptors or non-Edg receptors can regulate the malignant behavior of head and neck squamous cell carcinoma cells [38].

4.6. LPA and scleroderma

Scleroderma is a connective tissue disease characterized by a series of skin changes (inflammation, degeneration, thickening, fibrosis, sclerosis, and atrophy) in certain organs of the body [123]. Systemic sclerosis can also involve the digestive tract, lung, heart, and kidney in addition to the skin, synovial membrane and finger (toe) arteries [123]. Tokumura et al. [124] reported that serum levels of LPA were increased in patients with scleroderma. They found that LPA participated in the progression of scleroderma through regulation of fibroblast fibrosis. In a mouse model of scleroderma, LPA1 deficiency can decrease the degree of dermal fibrosis [125]. Johnson et al. [126] reported that during the progression of scleroderma, activation of the Rho/MRTF/SRF signaling pathway increased the expression of fibrosis-related genes such as *CTGF*, *ACTA2* and *COL1A2*. The activation of this pathway in scleroderma is reportedly mediated by LPA [127]. Fibroblasts differentiate into myofibroblasts and secrete a range of matrix proteins, which is an important pathological process of scleroderma. LPA-induced accumulation of myofibroblasts leads to an accumulation of these types of matrix proteins [125]. Remarkably, LPA is not only closely related to dermal fibrosis but is also involved in the regulation of fibrosis in organs such as the kidney, liver and lung [128–130]. LPA exerts its biological functions through the LPA receptor signaling pathway; therefore, LPA receptors can be used as new targets for the treatment of scleroderma. Selective inhibitors of LPA1 or LPA3 can decrease the degree of skin fibrosis in a mouse model of scleroderma by inhibiting the expression of TGF-β1, CTGF, MIP-1α, IFN-γ and collagen αl [125,131]. A phase II clinical trial confirmed that LPA1 receptor antagonists are effective in reducing skin fibrosis [132,133]. Since autotoxin is the major LPA-producing enzyme in the circulation, autotoxin inhibitors can reduce LPA levels and thereby exhibit an anti-fibrotic effect [34]. In addition, an LPA-IL-6-ATX-LPA amplification circuit exists in patients with scleroderma; that is, LPA can induce interleukin-6 to increase the expression of autotoxin, and the increased autotoxin further increases LPA. Inhibition of any component of this amplification circuit can improve the symptoms of skin fibrosis and, therefore, is a new strategy for the treatment of scleroderma [132].

4.7. LPA and skin inflammation

Skin is the largest organ of the inflammation reaction. LPA has been reported to induce the inflammatory reaction by activating the Jak-STAT signaling pathway [46–50]. Recent studies have revealed that LPA might serve as a trigger of skin inflammation. LPA induces the accumulation of macrophages, leukocytes and other inflammatory cells around wounds to promote wound healing [91]. Increased LPA in atopic dermatitis may lead to an increase in vascular permeability and may upregulate the expression of adhesion factors, thereby driving immune cells to migrate to the lesion [107,111]. In addition, LPA-induced IL-6 plays an important role in the skin fibrosis of scleroderma patients [132]. All these findings support an important role of LPA in skin inflammation responses.

5. Conclusions

Taken together, LPA is mainly catalyzed by autotoxin and PA-PLA1α/PA-PLA1β and is degraded by LPPs. LPA participates in the regulation of a variety of pathological and physiological processes in the skin by activating multiple signaling pathways through its receptors. Inhibition of LPA production, inhibition by specific LPA receptor antagonists or promotion of LPA degradation can inhibit LPA-mediated biological functions, which is likely a new strategy for the treatment of skin diseases. However, the metabolic pathways and regulatory mechanisms of LPA remain poorly understood. In addition, the roles and mechanisms of LPA in many skin diseases such as psoriasis, hemangiomas and systemic lupus erythematosus have not yet been explored. Therefore, more in-depth studies are required to investigate the roles and mechanisms of LPA during the progression of skin diseases.

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Conflict of interest

The authors have no conflict of interest to declare.

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