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Studies on lysophosphatidic acid action during in vitro preimplantation embryo development

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ABSTRACT

Assisted reproductive technologies, including in vitro embryo production (IVP), have been successfully used in animal reproduction to optimize breeding strategies for improved production and health in animal husbandry. Despite the progress in IVP techniques over the years, further improvements in in vitro embryo culture systems are required for the enhancement of oocyte and embryo developmental competence. One of the most important issues associated with IVP procedures is the optimization of the in vitro culture of oocytes and embryos. Studies in different species of animals and in humans have identified important roles for receptor-mediated lysophosphatidic acid (LPA) signaling in multiple aspects of human and animal reproductive tract function. The data on LPA signaling in the ovary and uterus suggest that LPA can directly contribute to embryo–maternal interactions via its influence on early embryo development beginning from the influence of the ovarian environment on the oocyte to the influence of the uterine environment on the preimplantation embryo. This review discusses the current status of LPA as a potential supplement in oocyte maturation, fertilization, and embryo culture media and current views on the potential involvement of the LPA signaling pathway in early embryo development.

1. Introduction

Assisted reproductive technologies, including in vitro embryo production (IVP), have been successfully applied to animal reproduction with the aim of developing breeding strategies for the improved production of valuable, healthy offspring. In addition to their role in breeding schemes, in vitro–produced embryos are also valuable for studying basic biological processes occurring during oocyte maturation, fertilization, and early embryo development. In addition, IVP techniques have significant value in the establishment of new biotechnologies, including stem cell culture, cloning by somatic cell nuclear transfer, and transgenesis, which in turn can find biomedical applications to create models for human disease and therapy. Despite the progress in IVP techniques over the years, further improvements in in vitro embryo culture systems are required for the enhancement of oocyte and embryo developmental competence. Oocyte competence is the ability of the oocyte to complete both nuclear and cytoplasmic maturation, ensure successful monospermic fertilization, undergo preimplantation development, and reach the blastocyst stage [1–4]. The developmental competence of oocytes is determined by the environment during in vitro maturation (IVM) [5,6], whereas culture conditions influence blastocyst quality [7,8]. In addition, maturation conditions impact the quality and preimplantation development of in vitro–produced embryos [9,10]. However, despite attempts to optimize IVP procedures, the

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quality of in vitro–matured oocytes and in vitro–obtained embryos is significantly lower than that of their in vivo–derived counterparts [5,11]. Thus, continued efforts to define the optimal media for IVP are still needed. The present review focuses on presenting the current knowledge of lysophosphatidic acid (LPA) as a potential supplement of oocyte maturation, fertilization, and embryo culture media and current views on the potential involvement of the LPA signaling pathway in early embryo development.

2. LPA structure and production

LPA (1- or 2-acyl-sn-glycero-3-phosphate) is a small glycerophospholipid (molecular weight, 430–480 Da) and one of the most potent lipid-signaling molecules. Studies on human cell lines have shown that LPA consists of 3 structural domains: a glycerol backbone, a single fatty acyl chain that is linked to the sn-1 or sn-2 site, and a phosphate group at the sn-3 position [12,13]. The phosphate group is suggested to be responsible for receptor activation, whereas the length and saturation degree of the carbon chain appear to be essential for the biological activity of LPA [13]. The most efficient molecular species of LPA includes a saturated 16:0 (palmitoyl) or unsaturated 18:1 (oleoyl) fatty acyl chain linked to the glycerol backbone by an acyl group [13].

To date, it has been shown that LPA can be synthesized both intracellularly as an intermediate in the synthesis of phospholipids and extracellularly as an intercellular signaling molecule [14,15]. The presence of LPA has been detected in various biological fluids, such as human and bovine serum and plasma [16–18], human saliva [19], ascites [20], follicular fluid [21], rat seminal plasma [22], and rabbit tears [23]. Moreover, LPA is produced and released by different cell types, including human erythrocytes [24], activated platelets [25], adipocytes [26], mouse neurons [27], bovine endometrial [28] and ovarian cells [29], and human ovarian and cervical cancer cells [30,31].

In the literature, 2 major pathways of LPA formation are described. In the first pathway, which is responsible for extracellular LPA production, phospholipids are metabolized by secreted phospholipase A_1 and A_2 (PLA_1 and PLA_2) to lysophospholipids such as lysophosphatidylcholine, lysophosphatidylserine, and lysophosphatidylethanolamine [16,17]. Lysophospholipids are then converted to LPA by autotaxin (ATX; lysophospholipase D [lysoPLD]), which is a key enzyme of LPA production in extracellular body fluids [16,17,21,32]. The second pathway is mainly involved in cellular LPA formation. In the first step, phosphatidic acid is produced from either phospholipids by phospholipase D (PLD) [31,33] or diacylglycerol by diacylglycerol kinase [34]. Subsequently, phosphatidic acid is deacetylated to LPA by the action of PLA_1 and PLA_2 [24,30,33]. Moreover, at least 2 additional methods of LPA synthesis are identified. LPA can be produced, mainly as a precursor for glycerolipid synthesis, through the acylation of glycerol 3-phosphate by glycerophosphate acyltransferase [35]. The phosphorylation of monoacylglycerol to LPA by monoacylglycerol kinase is implicated in another pathway for LPA production, either inside or outside the cells [34]. Circulating LPA has a relatively short half-life of approximately 3 min in mice [36]. However, LPA seems to be continuously produced and simultaneously degraded in blood on the minute scale [37]. For LPA stability and transportation in plasma, and from one cellular organelle to another, intracellular and extracellular lipid-binding proteins such as albumin, fatty acid–binding proteins, and gelsolin are required [38,39]. The various pathways of LPA synthesis contribute to multiple levels of regulation or dysregulation of LPA functions in different physiological and pathologic contexts in which LPA is implicated, including cancers [30,40,41], obesity [42], and pregnancy [43].

3. LPA receptor (LPAR)–mediated signaling

The biological actions of LPA are mediated by at least 6 high-affinity, transmembrane G-protein–coupled receptor types, LPAR1 to LPAR6 [44–47], and possibly through nuclear peroxisome proliferator-activated receptor γ [15]. These membrane receptors are encoded by distinct genes that have been described in humans as *LPAR1-6* and in mice as *Lpar1-6* [48]. LPARs exhibit high homology between species, such as human, bovine, ovine, porcine, and rodents. The highest homology has been identified between LPAR1 to LPAR3 because they belong to the endothelial differentiation gene family, and LPAR1 shares approximately 50% to 60% amino acid sequence identity with LPAR2 and LPAR3 [44,45,48]. In turn, homology in amino acid sequence between LPAR4 and LPAR1-3 amounts to 20% to 24%, whereas LPAR5 shares approximately 35% identity with LPAR4 and only 22% homology to LPAR1-3 [48]. LPAR4 and LPAR6 show similarity to P2Y purinergic receptors [48]. Non–endothelial differentiation gene family LPARs are predicted to bind LPA in an orientation that is similar to that reported for LPAR1-3 but through different amino acid residues that function in the recognition of LPA [49]. Finally, proliferator-activated receptor γ was identified as a nuclear receptor activated by intracellular LPA to form heterodimers with retinoid X receptors, regulating the transcription of various genes [15]. Biologically relevant concentrations of LPA, which range from 10 μM to 15 μM in human serum [16,21], are well over the apparent nanomolar Kd values that are needed to activate LPAR1-5 [48,50], implicating the importance of LPARs in physiological function. Only LPAR6 requires higher concentrations of LPA (up to 10 μM) to show an effect [48]. LPARs, through different distributions in organs and tissues and associations with different sets of heterotrimeric G-proteins, are able to activate diverse downstream signaling pathways, leading to gene regulation and LPA-induced cellular functions [44,46]. LPARs have been found in many reproductive tissues.

3.1. LPAR-mediated signaling in the ovary

Chen et al [51] demonstrated the messenger RNA (mRNA) expression of *LPAR1*, *LPAR2*, and *LPAR3* in human granulosa-lutein cells, whereas the expression of *LPAR4* was found in human ovary [46]. The expression of mRNA encoding *LPAR2* [52] and *LPAR4* [53] but not *LPAR3* [54] was found in mouse ovary. In turn, in bovine ovary, the