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Roles of Sphingosine-1-Phosphate in Reproduction

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Abstract

Sphingosine-1-phosphate (S1P) plays crucial roles in the regulation of cell growth, proliferation, differentiation, cell survival, migration, and angiogenesis. In the reproductive system, S1P protects mammalian germ cells from irradiation or chemotherapy-induced cell death in vivo and in vitro. Moreover, S1P could improve the survival rate of thawed ovary and transplanted ovary. Furthermore, S1P could improve the developmental potential of oocyte and preimplantation embryo. In conclusion, S1P plays important roles in reproduction.

Keywords

sphingosine-1-phosphate, ovary, germ cell, oocyte, preimplantation embryo

Introduction

Sphingolipids are complex lipids comprising a sphingoid base.[1] They were first described in the late 19th century and are one of the major lipid components of the cell membrane. Recently, sphingolipids are identified to not only regulate essential cell functions but also form cell membrane microdomain "lipid rafts" for integrating cell signaling.[2] Sphingolipids are involved in the regulation of cell growth and differentiation, death, migration, metabolism, and angiogenesis, among many other cell functions.[3–5]

Sphingolipid metabolites impact on membrane biology and as lipid second messengers modulate cellular homeostasis, functions, and responses to extracellular stimuli.[6] The main sphingolipid metabolites include sphingosine, ceramide (Cer), sphingosine-1-phosphate (S1P), ceramide-1-phosphate, and so on. Among these, S1P has emerged as a central regulator of mammalian biology. This review provides an overview of the biological characteristics of S1P and focuses on its roles in reproduction.

The Biological Characteristics of Sphingosine-1-Phosphate

Sphingosine-1-phosphate is an important bioactive sphingolipid. It is not only components of eukaryotic cell membranes but also pivotal bioactive-signaling molecule that regulates diverse biologic responses through extracellular and intracellular signaling.

Sphingosine-1-Phosphate Synthesis and Degradation

As other signaling molecules, S1P levels in the cells are tightly regulated by the balance between its synthesis and its degradation. Sphingosine kinase (SphK), which catalyzes the adenosine triphosphate -dependent phosphorylation of sphingosine, is a central regulating enzyme of S1P.[7] In mammals, there are 2 isozymes known as SphK1 and SphK2. The SphK1 is mainly localized in cytosol and SphK2 is predominantly localized in nucleus,[8] so they have different kinetic properties, tissue distribution, and temporal expression patterns, which indicate that they carry out distinct cellular functions and might be regulated differently.[9]

The degradation of S1P is mediated by 2 different pathways: one is the reversible dephosphorylation back to sphingosine by specific S1P phosphatases (S1P phosphatases or type 2 phosphatidate phosphohydrolases) and the second is the irreversible degradation in endoplasmic reticulum by a pyridoxal phosphate-dependent S1P lyase (SPL) to hexadecenal and ethanolamine phosphate, which are subsequently reused for the biosynthesis of phosphatidylethanolamine.[10,11]

Extracellular and Intracellular Signaling of S1P

Sphingosine-1-phosphate plays important roles in diverse physiological and pathological processes in mammalians. It regulates

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cell growth, proliferation, differentiation, cell survival, migration, and angiogenesis.[12–15] The most important biological role of S1P is to function as a ligand for a family of G-protein-coupled receptors called S1PR1-S1PR5.[16,17] They are ubiquitously expressed and couple to various G proteins that regulate numerous downstream signals.[9,11,18] This process—agonists activate SphK1 and induce its recruitment to the plasma membrane, producing S1P to activate S1PRs—is called "inside-out signaling."[19,20]

Besides acting extracellularly through its cell surface receptors, S1P also acts as a second messenger to mediate several cellular functions, such as cell survival, proliferation, autophagy, and calcium homeostasis.[9,21] Early studies demonstrated that S1P could induce calcium release from the endoplasmic reticulum.[22] Recent studies found that S1P bound and altered the function of several disparate intracellular proteins, such as histone deacetylases,[23] tumor necrosis factor (TNF) receptor-associated factor 2,[24] protein kinase C δ,[25] prohibitin 2,[26] and β-site amyloid precursor protein cleaving enzyme 1.[27]

Roles of S1P in Reproduction

In sphingolipid metabolites, S1P plays important roles in cell survival and proliferation, whereas Cer activates the intrinsic and extrinsic apoptotic pathways through receptor-independent mechanisms. Therefore, the cellular balance of these sphingolipid metabolites forms the "sphingolipid rheostat," which addresses the importance of balance of these mediators and not the absolute amount of metabolites in determining cell fate.[28] In reproductive system, S1P seems to protect the germ cell from apoptosis in vivo and in vitro and improve the developmental potential of oocyte and preimplantation embryo.

Roles of S1P in Male Germ Cell

Previous studies reported that northern blot analysis indicated S1PR2 and S1PR3 at medium expression levels, S1PR1 barely detectable, and S1PR4 and S1PR5 undetectable in the adult mouse testis,[29] and real-time reverse transcriptase–polymerase chain reaction detected S1PR1, S1PR2, S1PR3, and S1PR5 in mouse spermatozoa[30];moreover, S1PR1 and S1PR2 were detected by immunohistochemistry in human Sertoli cells, with occasional and weak staining in the spermatogonia and early meiotic spermatocytes.[31]

Sphingosine-1-phosphate seems to be a survival factor in male germ cells. The S1P partially protected the very early stages of mouse spermatogenesis from irradiation-induced apoptosis[32] and inhibited human germ cell apoptosis in a culture of human seminiferous tubules.[31] Moreover, disruption of S1P lyase, which degrades S1P and regulates the ratio of Cer and S1P, resulted in reduced testis size in *Drosophila*, which is caused by increased apoptosis.[33] In addition, S1P induces exocytosis through a G_i-coupled receptor triggering a complex signaling pathway leading to Rab3A activation and membrane fusion in the process of acrosome reaction.[34]

In summary, S1P inhibits apoptosis in 2 ways: one is through activating extracellular signal-regulated kinase and inhibiting c-Jun N-terminal kinase through the S1PRs and G-protein-coupled receptors,[15,35] and the other is through intracellular signaling, where exogenous S1P could upregulate antiapoptotic Bcl-2 as well as downregulate proapoptotic Bad and Bax.[36,37] In male germ cells, S1P inhibits apoptosis possibly by inhibiting nuclear factor kappa B and activating protein kinase B (AKT).[31]

Roles of S1P in Ovary

The central functional unit of the ovary is the follicle, a structure composed of a single germ cell (oocyte) surrounded by one or more layers of specialized somatic cells called granulosa cells, and each follicle is enveloped by a basal lamina, a specialized sheet of extracellular matrix that separates the internal follicle from the theca cells.[38] Immunohistochemistry demonstrated that in hen and human ovarian tumors, S1PR1 was expressed in endothelial cells of blood vessels and immune cells.[39] The expression of S1PR1, S1PR2, S1PR3, and S1PR5 but not S1PR4 were found in primary human granulosa lutein cells and the granulosa lutein cell line HGL5 cells.[39] The S1P was detected in the associated with follicular fluid high-density lipoproteins (FF-HDLs) in the human follicular fluid obtained from women undergoing ovarian hyperstimulation.[40] Since angiogenesis plays an important role in the development of the ovarian follicle and its subsequent transition into the corpus luteum, the S1P in follicular fluid and its role in angiogenesis are important in ovarian function.[40] The corpus luteum is a transient endocrine gland that are formed after ovulation from the remaining wall of the ovarian follicle. Its main function is to secrete steroid hormone progesterone, which is essential for implantation of the blastocyst and maintenance of pregnancy.[41] The FF-HDL-associated S1P promotes granulosa lutein cell migration via S1PR3 and RAC1 activation, which may represent a novel mechanism contributing to the development of the corpus luteum.[39] The S1P blocks the luteolytic effect of prostaglandin F-2α by decreasing the activities of caspase 2, 3, and 8 and increasing AKT phosphorylation and TNF-α expression in the pregnant rat.[42] In ovarian transplants, S1P promoted neoangiogenesis and reduced ischemic reperfusion injury.[43]

Anticancer treatments can lead to premature ovarian failure and infertility. Radiation-induced oocyte loss was prevented by in vivo therapy with S1P in mouse.[44] Long-term follow-up studies from in vivo mating trials have confirmed that S1P indeed preserves a normal level of fertility in the face of cancer therapy, at least in female mouse.[45] In mouse, local application of S1P also protected ovarian follicles from chemotherapy-induced cell death.[46,47] Preadministration of S1P into ovarian bursa had protective effects on whole-body irradiation-induced apoptosis of primordial follicles in rats.[48] Recent study reported that females given S1P or the S1P mimetic-FTY720 by direct intraovarian cannulation for 1 week prior to ovarian irradiation rapidly resumed menstrual cycles due to the maintenance of follicles.[49] They also found that monkeys given FTY720 prior to ovarian irradiation also became pregnant in the mating trials, and offspring conceived and delivered by radioprotected females developed normally and showed no

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evidence of genomic instability as measured by micronucleus frequency in reticulocytes; moreover, adult human ovarian cortical tissue xenografted into mice also exhibited a reduction in radiation-induced primordial oocyte depletion when preexposed to S1P.[49]

Preservation of an intact primordial follicular pool is important in the cryopreservation program because it could represent the ovarian reserve. The addition of 20 μmol/L S1P into the cryopreservation media did not improve ovarian or vascular tissue survival by the slow-freezing method.[50] However, Jee BC et al reported that supplementation of 2 μmol/L S1P into vitrification media had a significant effect on the integrity of primordial follicles from vitrified–warmed ovarian grafts.[51] This contradiction needs further research.

In summary, protecting oocyte from apoptosis is involved in the antiapoptosis function of S1P, but improving the growth rate of follicle, accelerating the formation of corpus luteum, and increasing the survival rate of transferred ovary refer to the proliferation and angiogenesis function of S1P. Several studies have indicated that S1P increases DNA synthesis and cell division in diverse quiescent cell types. [52–54] This S1P-induced cell proliferation is inhibited by different G proteins inhibitors, which indicates that the effects of S1P on cell proliferation are through extracellular receptors and G-protein-coupled receptors.[55] Phospholipase D (PLD), phosphatidylinositol 3-kinase (PI3K), and AKT are known to be involved in cellular signaling related to cell survival and proliferation. The S1P stimulation of S1PR3 overexpressing in Chinese hamster ovary cells but not vector-transfected cells induced activation of PLD, PI3K, and AKT in a time- and dose-dependent manner.[56] The S1P stimulates cell proliferation and migration, which are required for inducing angiogenesis. The S1P induces vascular endothelial growth factor production in endothelial cells and enhances endothelial cell migration, which promotes blood vessel formation.[57,58] Knockout studies demonstrated that S1PR1 is a crucial receptor in mediating angiogenesis.[59] The S1PR1 also plays an important role in the maintenance of endothelial and epithelial barrier integrity in conjunction with S1PR2 and S1PR3 to increase vascular integrity.[60–62]

Roles of S1P in Oocyte and Preimplantation Embryo Development

The protective role of S1P on oocytes has at least 2 aspects: one is decreasing oocytes apoptosis and the other is improving the developmental potential of oocytes. Extracellular S1P could inhibit the apoptosis of mouse mature oocytes induced by doxorubicin cultured in vitro.[47] Trafficking of Cer from the cumulus cells was not affected by S1P, but S1P specifically interfered with Cer-promoted oocyte death.[63] The S1P could not only protect bovine oocytes from a physiologically relevant heat shock but also affect oocyte maturation in the absence of heat shock.[64,65] The blastocysts from S1P-treated oocytes which survived heat shock had a normal developmental potential as determined by caspase activity, total cell number, and percentage of apoptotic cells.[65] It was suggested that S1P may be used to improve fertility in situations where developmental competence of the oocytes was compromised. Immature mouse oocytes were incubated in maturation medium with S1P, the blastocyst formation rate was higher, and the percentage of apoptotic blastomeres was significantly lower, than those of the control group.[66] A recent report indicated that addition of S1P to human oocyte culture medium significantly reduced fertilization rate although such treatment decreased embryo fragmentation.[67] Ceramide decreased the mouse blastocyst formation rate and induced embryonic cell apoptosis, but S1P partly inhibited the effect of Cer during the mouse preimplantation embryonic development.[68]

In summary, the developmental potential of oocyte and embryo cultured in vitro is to be affected greatly by the environment. The S1P may decrease the effects of the unfavorable factors in in vitro culture and stimulate the development of the embryo by the extracellular- and/or intracellular-signaling pathway.

Summary

Currently, assisted reproductive technologies (ARTs) have been widespread used in the world. However, there are some problems in this field, such as the low developmental potential of oocyte from cryopreservation and in vitro maturation, the low survival rate of follicles from cryopreservated ovary after transfer, and the much fragment and low developmental potential of embryo from in vitro fertilization. Previous studies have indicated that S1P may solve these problems in ART, but whether S1P improves the survival rate and the developmental potential of oocyte and embryo in ART is not known. More studies on the functions and mechanisms of S1P signaling in the physiological and pathological processes of reproduction and the safety of S1P are needed.

Declaration of Conflicting Interests

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