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Brief Commentary

Bioactive lipid: A novel diagnostic approach for retinoblastoma in clinical management

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ABSTRACT

Bioactive lipids, presumably lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P), play a critical role in regulating an array of cellular functions ranging from cellular fate determination, inflammation, immunity, and cancer. Epidemiological evidence suggests that both the metabolites play a prominent role in the development and progression of oncogenic phenotype in a variety of cancers including breast, colorectal, pancreatic, and lymphoma. Previous studies have demonstrated the possible association of LPA, S1P and their receptor in regulating the pathogenesis of retinoblastoma, however, the exact mechanism involved in this event has not been studied in detail. Importantly, understating the mechanistic basis of LPA and S1P regulation is of utmost significance, as far the phenotypical complexity of retinoblastoma (RB) is concerned. Findings from the recent investigations elucidate the prospective role of S1P in provoking the chemoresistant behavior of RB cells for etoposide. In this context, the current paper will enable the identification of novel diagnostic biomarkers and therapeutic targets for better treatment and clinical efficacy in children with RB.

Keywords: Bioactive lipids, Cancers, Lysophosphatidic acid, Retinoblastoma, Diagnostic marker

BIOACTIVE LIPID

Bioactive lipids served as a potent intra- and extracellular effector molecule regulating several biological processes encompassing cell cycle, survival, apoptosis, and migration. LPA and S1P have been involved in the development and progression of a variety of cancers including breast, colorectal, pancreatic, and lymphoma.[1,2] Interestingly, both compounds also mediate cell survival, migration, angiogenesis, and chemoresistance by altering the expression of p53, HIF1-α, Bcl-2, VEGF, and MMPs.[2] To date, six GPCR-like receptors, namely, LPA receptors (LPAR) 1–6 in human have been identified for LPA signaling molecule. Extensively reviewed LPAR 1–3 belongs to endothelium differentiation gene EDG receptor and has high affinity for LPA while three are recently reported belongs to non-EDG receptor LPAR4, LPAR5, and LPAR6 that serve as a low-affinity surface receptor.[3,4] There are also five specific S1P receptors (S1P 1–5) for the S1P extracellular ligand that mediates the distinct cell signaling pathways.[5] Since the discovery of the different family of LPA and S1P receptors, there has been several LPA analogs which have generated that function as agonist/antagonist for LPA and S1P receptors. The potential agonist of highly reviewed LPA 1-3 receptors such as 1-oleoyl LPA, Alkyl LPA, 1-oleoyl-2-O-methyl-rac-glycerophosphothionate, N-palmitoyl serine phosphatidic acid, dodecyl fatty alcohol phosphate, and N-acyl aminoethanol phosphoric acid (NAEPA 11,17,19) and antagonist VPC12249, VPC32183, dioctylglyceropyrophosphate,

NSC161613, and Ki16425. These pharmacological tools in the form of agonist/antagonist function as specific therapeutic drugs in different pathophysiological conditions.

RETINOBLASTOMA (RB)

In India, the major reason behind the mortality in children is malnutrition but death due to cancer such as RB cannot be neglected. RB is one of the most common neoplasms of an eye in childhood and accounts for 3% of all childhood malignancies worldwide.[6] The phenotype is caused by a mutation of the RB1 gene in a developing retinal cell which was later described as the first tumor suppressor gene.[7] Although the disease is characterized by several symptoms, the incidence of chalk-like calcification with leukocoria and reflection like a white mass in the retrolental is prominent.[8] The retina is the sensory membrane that lines the inner surface of the back of the eyeball and is composed of several layers including specialized cells bearing photoreceptors. These regions are meant for the conversion of light signals to neural signals for visual recognition. A higher incidence of the disease is observed in Africa, India, and native America.[9] Although RB is rare, its early onset in young children and late-stage diagnosis with poor outcome makes it clinically relevant for study. It was estimated that every two-thirds of children are diagnosed before 2 years and 95% before 5 years of age.[10] Furthermore, due to its high prevalence in India, still lacking specific diagnosis guidelines pose a serious issue as far as the therapeutic efficacy is concerned.[11] In addition, findings from Rangamani *et al*. revealed incidence rates of RB from population-based cancer registries (PBCRs) of Bengaluru, Mumbai, Chennai, Delhi, and Kolkata using the data from the National Cancer Registry Programme.[12] The data show that RB occurrence is 78% in females and 81% in males of pooled cases from five PBCRs.[12] The current scenario of RB treatment includes chemotherapy followed by enucleation shown to be ineffective in different age groups. Interestingly, the mechanistic underpinnings and the molecular profile of intraocular tumors are not completely elucidated, especially in the Asian-Indian population. Therefore, it is considered as one of the most complicated malignancies in the Indian population with a perspective to clinical management. For these reasons, a standard therapeutic approach with specific guidelines needs to be seriously realized and implemented not only to cure the disease but also to preserve vision with minimal long-term side effects. Despite the identification of the potential role of LPA and S1P in the regulation of retina pigment epithelial cells function, their potent role in the development and progression of RB is yet to be established.

THE POSSIBLE IMPLICATION OF BIOACTIVE LIPID IN THE DEVELOPMENT AND DIAGNOSIS OF RB

Altered regulations of lipid mediators result in several pathological conditions such as cancer, arthritis, cardiovascular diseases, gastrointestinal diseases, neurological disorders, renal dysfunction, and immune disorders.[13] Research from the past three decades has shed light on the involvement of lipid mediators in the pathogenesis of different diseases including RB by provoking various biochemical networks and signaling pathways. LPA and S1P in response to oncogenic signals activate their receptors and play a key role in the regulation of oncogenic phenotype in RB[14] [Figure 1]. Although there are limited findings about the prospective role of LPA and S1P on retinal function, subsequent studies show that possible binding of LPA to its receptor (LPAR)[15] plays a crucial role in retinal pigment epithelium (RPE) cells. Furthermore, findings from Thoreson *et al*. have reported the activation of non-selective cation currents in rat RPE cells through the MAP kinase signaling pathway by LPA. The subsequent finding shows that LPA stimulates RPE cell proliferation through activation of its receptors.[16] Evidence from Yang *et al*. have reported LPA mediates retinal ganglion cell degeneration in oxygen-induced retinopathy through LPA1.[17] Recently, Lidgerwood *et al*. have demonstrated the impact of LPA on human RPE cells.[18] They have reported LPA maintains the integrity and functionality of the healthy retina and blood retinal barrier. Similar to this S1P has also been observed in the function of retina pigment epithelial cells. A study by Terao *et al*. has shown the role of S1P in angiogenesis, inflammation, and barrier integrity in choroidal neovascularization through its receptors S1P2 and S1P3.[19] Another study by Porter *et al*. showed the novel expression of S1P sphingosine kinases and S1P receptors in ocular tissues.[20] The expression of S1P synthesizing enzyme and receptors, SPHK1, S1PR2, and S1PR3, increased immediately after light damage that suggests their crucial function in apoptosis or light stress

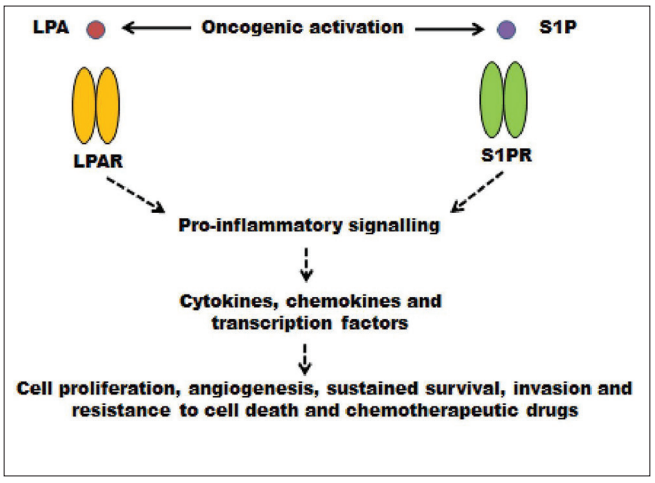

Figure 1: During oncogenesis bioactive lipids LPA and S1P bind to their respective receptors and mediate activation of inflammatory signals leading to the release of various cytokines and chemokines that play a crucial role in the development and progression of cancer.

responses in the eye. Recently, Kakkassery *et al*. have shown the possible role of the S1P axis in the development of chemoresistance in cell lines of RB.[21] They observed the effect of etoposide on selected bioactive lipids in both the prenatal RB cell line WERI Rb1 and subclones which are etoposide resistant WERI EtoR and found an increased level of sphingosine in both the cell lines. Further, they also found that S1P promoted survival and favored etoposide resistance in RB cells WERI EtoR suggesting the involvement of S1P in the generation of chemoresistance in RB. An elevated level of LPA and S1P was observed in glaucoma, open-angle glaucoma, proliferative diabetic retinopathy, and retinal vein occlusion which are collectively considered retinal diseases. Accumulating evidence shows the critical role of bioactive lipids, especially LPA and S1P in the function of the retina.[17-20] As reported previously, both LPA and S1P have the potential to stimulate the oncogenesis and aggravate the excruciating phenotypical complexity in RB.[22] Unfortunately, decades of research have failed to develop such guidelines, prognostic and diagnostic strategies in general and explore the mechanistic role of LPA and S1P in the progression of RB which can be used as a therapeutic biomarker in particular. Nevertheless, the role of LPA and S1P in children with RB cannot be undermined, thus needs to be evaluated shortly for possible biomarker discovery and therapeutic potential.

THE IMPLICATION FOR THERAPEUTICS IN FUTURE

The critical role of mechanistic basis and oncogenic promoting phenotype of LPA and S1P in tumor metabolism is less studied and poorly understood. Due to the invasive properties during cancer progression and development, these bioactive molecules play a key role in alterations of lipid metabolism to cancer signaling. Moreover, tumor heterogeneity and dysregulated lipid metabolism exceedingly necessitate and may enforce the adoption of the anticancer therapy by targeting the LPA, S1P, and their receptors. Furthermore, an effective strategy must be adopted for the development of an ideal biomarker with high specificity to assess the clinical severity of RB. Numerous cancers including RB are characterized by altered LPA receptor-mediated signaling. Therefore, understanding the basis of regulation and behavior of LPA and S1P signaling in RB needs to be explored. This will not only overcome the disease burden of childhood RB but also improve the diagnostic potential and clinical armamentarium.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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