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Review Article

Signaling Pathway Governed by Lipid Derived Molecules as Secondary Messenger

Debopriya Kundu[1] and Kalpataru Halder[2*]

[1]Post Graduate Department of Botany, Brahmananda Keshab Chandra College, 111/2 B. T. Road, Kolkata-700108, India
[2]Department of Molecular Biology & Biotechnology, Brahmananda Keshab Chandra College, 111/2 B. T. Road, Kolkata-700108, India

Correspondence E-mail: kalpataruhalder@outlook.com

Abstract

Research shown that the cell death, particularly apoptosis, can extend beyond single cell boundaries. Gap junctions IP3 diffusion, and sphingolipids play significant roles in membrane biology and regulation of cell function. S1P plays crucial role in the cardiovascular and immune systems, serving as a mediator of signaling during cell migration, differentiation, proliferation, and apoptosis. Intestinal phospholipid metabolism, including 1B phospholipase A2 and autotaxin-mediated pathways, contributes to cardiometabolic diseases through multiple mechanisms.

A potential strategy for treating cardiovascular and metabolic diseases is the therapeutic suppression of1B phospholipase A2 and autotaxin in the gastrointestinal tract. Cellular stress signalling, inflammation, resolution, and host defence responses are all significantly influenced by lysophospholipids such LPA and S1P. New therapies for cancer, vascular diseases, fibrotic disorders, and autoimmune diseases have been made possible by developments in lysophospholipid research.

Keywords: - *Apoptosis, Phospholipids, IP3, Sphingolipid*

Introduction

Cell death is a process which is transferred to healthy cells associated to the dying cell, called bystander death. Cell-to-cell connection is fixed by plasma membrane channels known as GJs. Gap junction permits the route of small molecular weight molecules, such as glucose, glutamate, glutathione, cAMP, ATP, IP3, and ions. The passage of Ca^{2+} messenger Inositol Triphosphate through gap junction is critical for intercellular cell death, and targeting this intercellular pathway is crucial for preventing exaggerated cell death (Nielsen, et. al., 2012).

S1P is a natural bioactive lipid molecule that plays crucial role in the cardiovascular and immune systems, which is a chemokine that participates in chemotaxis and is involved in various processes in the human body. S1P is regulated by SPL and SPP1/2, which regulate histone acetylation. S1P secretion is strictly controlled by SPL or dephosphorylated by SPP1/2 (Bravo, et. al., 2022). Sphingosine-1-phosphate related enzymes are future objectives for treating bone disorganization. 5 different Sphingosine-1-phosphate receptors have been recognised and encrypted by Edg 1, 5, 3, 6, and 8. The development of S1P agonists and antagonists has broadened our understanding of S1P, but figuring out a method to inverse excess osteolysis without having an impact on bone turnover is crucial for reversing osteolysis (Blaho, et. al., 2014). Upcoming research directions, drug targets are essential for advancing this therapeutic target.

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Lysophospholipids are lipids with a single fatty acid chain. They are classified by their polar head structure.These lysophospholipids are termed as lysophospholipid mediators. Lysophospholipids have various pathophysiological functions, including regulation of arterial ring contraction and modulation of systemic blood pressure.

Recent findings on S1P have been characterized, with S1PR1 being the first and four additional S1PRs The objective of the study is to comprehend the cellular reactions, development, method of operation, and activity of these lysophospholipids in the diagnosis of illness in various systemic organs.

IP3: Most significant variable in intra- and intercellular Ca^{2+} signalling

One of the most significant improvements in our understanding of what mechanisms do cells use to chemically transfer incentives across the membrane of a cell to intercell Ca^{2+} elevations can be attributed to the Inositol Triphosphate's identification as second messenger roughly thirty years earlier (Gambardella, et. al., 2021). Many external stimuli interact with plasma membrane receptors to initiate the PLC enzyme's action. There are thirteen distinct Phospholipase C isoforms, that are separated into 6 modules evaluating structural similarities: phospholipase C-β , phospholipase C-γ , phospholipase C-δ, phospholipase C-ε, phospholipase C-ζ and phospholipase C-η. They are activated by a number of different pathways (fig 1), such as activation of Ras, activation of receptor and non-receptor tyrosine kinases, stimulation of GPCRs, and an increase in cytoplasmic Ca^{2+} concentration (Bill and Vines, 2020).

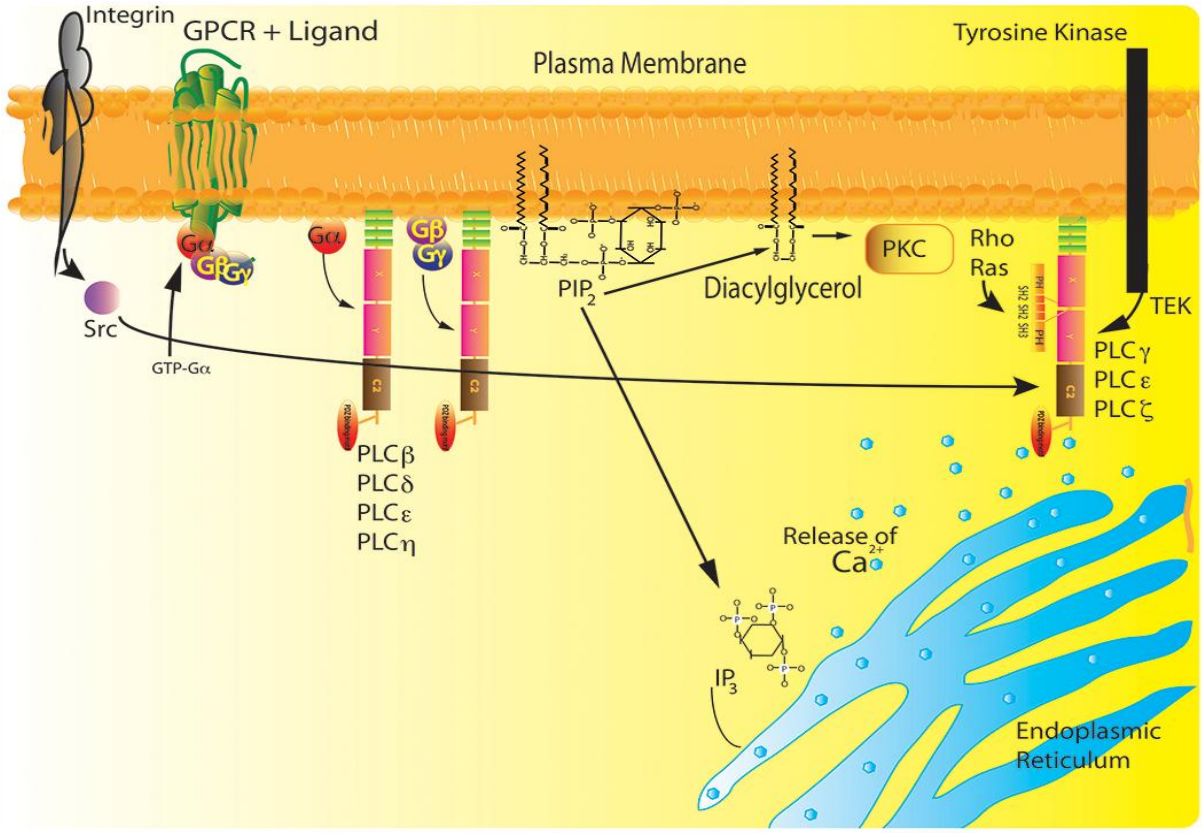

Fig 1: Phospholipase C (PLC) activation can be initiated through various pathways involving tyrosine kinase receptors, T-cell receptors, B-cell receptors, Fc receptors, Integrin adhesion protein or G-protein coupled receptors. These pathways are triggered by specific ligands, such as neurotransmitters, histamines, hormones and growth factors, leading to signalling cascade and mobilization of Ca^{2+}. However for simplicity this figure illustrates PLC activation only through integrins, GPCRs and tyrosine kinase receptors. (adapted from Bill and Vines, 2020)

Phosphoinositol-4,5-bisphosphate is broken down by PLC into diglycerides and Inositol Triphosphate. The following spreads throughout the cytoplasm attach to its receptor that is mostly found on the ER, which is the greatest and most in controlled intercell Ca^{2+} source (Spolaor et al, 2022). The protoplasmic Ca^{2+} rises that follows a variety of configurations that are highly organised. For example, oscillations can manifest as localised, repeating Ca^{2+} spikes, and localised Ca^{2+} increases can be amplified to create spreading waves. Almost all cell types, including excitable and non-excitable cells, have a flexible signalling mechanism that is based on this spatiotemporal organisation (Spolaor, et. al., 2022; Sayedyahossein, et. al., 2023). In order to effectively control a wide range of physiological processes, including muscle contraction, endothelial permeability, apoptosis, neurotransmitter release, secretion, immune responses, and many others, the Ca^{2+} signalling system must be endowed with sufficient dependability and specificity (Case et. al., 2007; Yuan, et. al., 2020). Information is encoded in the amplitude, spike length, and frequency of repetitive oscillating Ca^{2+} spikes (Ruffinatti et. al., 2020). Contrarily, single Ca^{2+} transients typically remain longer, and the ensuing signal typically manifests as a cytoplasmic Ca^{2+} wave. GJs and paracrine signalling both have the ability to communicate Ca^{2+} waves between cells. IP3 is regarded as the most important coordinating messenger because Ca^{2+} passage across Gap Junctions is recognised to be inhibited because cytosolic Ca^{2+} binding proteins are available (Churchill and Louis, 1998; Pawar et. al., 2023). In comparison to Ca^{2+}, IP3 has a 100 times greater GJ permeability and a significantly greater effective diffusion constant (283 µm 2/s contrary to 13 to 65 µm 2/s) (Pawar et. al., 2023; Hofer et. al., 2002). The paracrine and gap junctional pathways (Scemes et. al., 2000; Tirosh et. al., 2021; Liang et. al., 2020) are frequently responsible for maintaining intercellular wave propagation, which is additionally aided by regeneration processes. Ca^{2+} oscillations are additionally manipulated by both GJs and HCs.The frequency of spikes, the proportion of cells exhibiting **Ca^{2+}** oscillations, and the synchronisation of **Ca^{2+}** oscillations are all known to be modulated by GJs (Clair et. al., 2011; Turovsky, et. al., 2021). Through way of stimulation of several recreative signalling loops, which begin with Ca^{2+}-induced HCs opening followed by the release of adenosine triphophate or NAD or the uptake of Ca^{2+} through open HCs, HCs appear to be associated in the occurrence of Ca^{2+} oscillations (Verma et. al., 2009).

IP 3 receptors, the ER, and mitochondria collaborate: promote intracellular Ca 2+ signalling.

Ca^{2+} signals' spatiotemporal organisation is heavily influenced by (i) the traits and (ii) the locations where the Ca^{2+} release channels are active.The IP3R is a tetramer, and each subunit consists of a suppressor domain and an IP3-binding core located in the cytoplasm, a six transmembrane domain located at the C-terminus (Foskett, 2007).The follwing is obligate for mediating the signal of ligand binding's transition from the inositol triphosphate-binding domain to the channel domain. Additionally, following domain keeps the inactive Inositol triphosphate receptor channel closed and includes numerous destrinations for IP3R activity controller (fig 2) (Foskett et. al., 2007; Parys et. al., 2012). In many various kinds of tissues and organs, IP3Rs are highly expressed. It should be noted that the receptor's isoform (IP3R1, IP3R2, or IP3R3) determines the receptor's affinities for IP3 binding and its sensitivity to modulatory signals (Gambardella et. al., 2021). The most well-known regulatory factor is $[Ca^{2+}]_i$, which acts on the receptor in a biphasic manner: Ca^{2+} activates it at low density (100-300 µM), but when it reaches higher concentrations (beyond 300 µM), it becomes inhibitory (Zhang et. al., 2020, Eraso-Pichot et. al., 2023). Active mitochondria contribute in modulating the Ca^{2+} signalling , which is related to the spatial organisation of IP3Rs (Groten et. al., 2022, Pizzo et. al., 2012). Protons are extruded by mitochondria to generate difference in charge and chemical concentration across a membrane that facilitates adenosine triphophate production. When mitochondria are in areas with high Ca^{2+} concentrations, they can collect Ca^{2+} more efficiently (Rizzuto et. al., 2009; Jimenez et. al., 2022). Several studies have shown that IP3Rs can be concentrated at specific sites along the ER and in the vicinity of mitochondria (Malik, et. al., 2021, Bononi et. al., 2012). It is said to take more than 16 µM $[Ca^{2+}]_i$ for mitochondrial Ca^{2+} uptake to be fully activated (Higo et. al., 2010). A suitable gap between the IICR site and the mitochondria is required by the uptake system (Deegan et. al., 2013). The MAM is the term used to describe the physical connection between the ER and mitochondria (Madhamanchi et. al., 2022, Patergnani et. al., 2011). A variety of proteins, including chaperone

proteins like the grp 75 and mitofusin-1 and -2 form structural interactions that are necessary for the interaction between the ER and the mitochondria. The latter improves mitochondrial Ca^{2+} accumulation by directly connecting VDAC1 and the IP3R (Szabadkai, et. al., 2006).

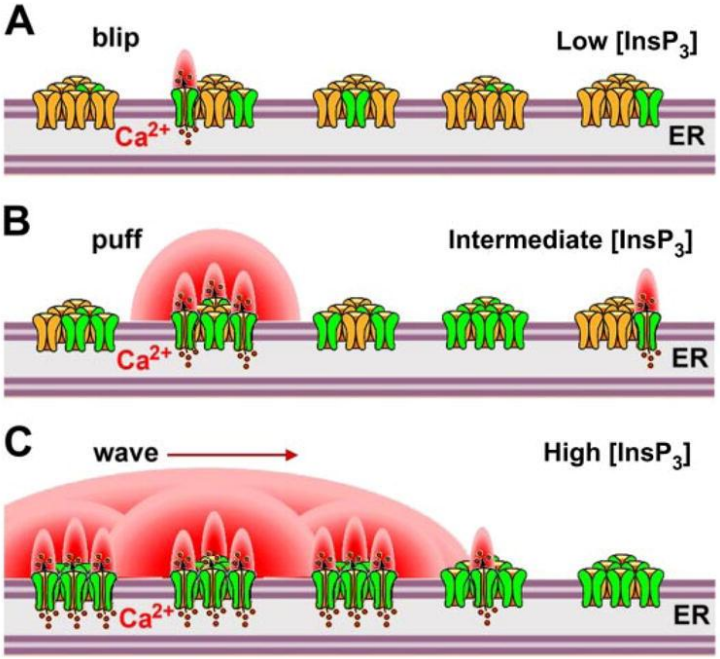

Fig 2: This schematic representation illustrates how IP_3 receptor channels responding to differing IP_3 concentratons, resulting distinct pattern of Ca^{+2} signaling, ranging from localized signal ("blip") to coordinated activations within clusters and eventually leading to global Ca^{+2} wave (Adapted from Foskett, et. al., 2007)

IP3: from a means of survival to a brutal murderous

The role of Endoplasmic Reticulum and mitochondria in programmed cell death

Restricted Ca^{2+} rising are essential for normal growth and development of cells an ongoing elevation is generally recognised to cause cell death (Sammels et. al., 2010). It turns out that the role of Ca^{2+} in cell death is quite complicated.Ca^{2+} does not lead directly to cell death; instead, the path includes the interaction of numerous systems, activating various aspects of the cell death programme. The regulation of cell death is significantly influenced by transform in Ca^{2+} circulation throughout intercell Ca^{2+} chambers, particularly the Endoplasmic reticulam. First, changes in ER Ca^{2+} pool can have an impact on chaperones and impair protein folding, which can result in ER stress. The improperly folded proteins that have accumulated in the ER are then removed by starting an unfolded protein response (Costas-Ferreira, et. al., 2021). Autophagy is a catabolic cellular programme that makes it easier to remove damaged proteins, and ER stress can trigger it. However, under extreme stress, these signals become harmful and can trigger necrosis or apoptosis (Madhamanchi et. al., 2022, Deegan et. al., 2013). The mitochondria is capable of identifying ER Ca^{2+n} release, which causes mitochondrial Ca^{2+} overload and death (Huang et.al., 2022). Without the need for an overall rise in **Ca^{2+}** i or store-operated Ca $^{2+}$ entry, it has been demonstrated that ER Ca^{2+} release alone is sufficient to cause apoptosis (Yang et. al., 2021, Lindner et. al., 2020). Changes to the ER luminal Ca^{2+} concentration can also change the sensitivity of cells to apoptosis (Rosa et. al., 2022). Furthermore, the ER and mitochondria are in extremely close contact to one another, which increases the risk of Ca^{2+} excess and increases the likelihood of death in the cells (Costas-Ferreira, et. al., 2021). The proapoptoticCa^{2+} transport between the ER and the mitochondria has recently been linked to Inositol Triphophate Receptor subtype 3, not Inositol Triphophate Receptor subtype 1, and voltage dependent anion channel 1 in the Mitochondria associated ER membrane (De Stefani et. al., 2012, Oh, 2023). Cell destiny appears to be significantly influenced by the strength of the Ca^{2+} signal that mitochondria

receive. By increasing mitochondrial energy production or by promoting the transcription of particular genes (Cardenas et. al., 2010, Morciano et. al., 2018). However, a sudden rise in mitochondrial **Ca^{2+}** leads to the permeability transition pore (PTP) opening, which unexpectedly increases the IMM's permeability. Osmotic stresses cause the matrix to swell, which causes mitochondria to depolarize, impede the respiratory chain, produce reactive oxygen species (ROS), remodel the IMM, and ultimately cause the OMM to permeabilize. When this occurs, a number of proapoptotic molecules, including Cytochrome C (CytC), SMAC/Diablo, and apoptosis-inducing factor, are released into the cytosol (Kroemer et. a., 2007, Rasola et. al., 2011). The immediate appearance of the distinctive morphological characteristics of apoptosis depends on the following activation of an exclusive group of cysteine proteases. When Ca^{2+} signal ceases, PTP can be closed once more, restoring ATP synthesis and mitochondrial metabolism (Szalai et. al., 1999). The intercell Adenosine triphosphate content is widely acknowledged as an essential parameter in establishing the mechanism of apoptosis. Energy is needed for the process of apoptosis (Szalai et. al., 1999, Rasola et. al., 2011). Notably, healthy intact cells have also been found to exhibit quick oscillation between the Protein tyrosine phosphatases active and inactive states, suggesting a greater physiological function for its opening (Cannino et. al., 2022). On the PTP's molecular appearance, little is known. It has long been believed to be made up of the voltage dependent anion channel (in the Outer mitochondrial membrane), the ANT; carrier in the Inner Mitochondrial Membrane), mitochondrial CypD, and a number of various proteins. Presently, it remains uncertain whether the voltage-dependent anion channel, Adinosine nucleotide translocase, or even the outer mitochondrial membrane are integral components of PTP for channel formation (Kim, et. al., 2023, Kharechkina, et. al., 2023). Despite this, the exact mechanism of their participation are yet to be fully understood. The oligomers might create pathways which would then allow lipid pores to permeabilize it (Roy, et. al., 2010, Tait and Green, 2010). It has also been demonstrated that Bcl-2-associated X protein and Bcl-2 homologous antagonist/killer interact with VDAC, control its characteristics, or group together as higher-ordered compounds (Yu, et. al., 2007, Shoshan-Barmatz, et.al., 2010). Different Bcl-2 family members may regulate VDAC. Additionally, VDAC oligomers seem to play a crucial role in the cytoplasmic membrane's discharge of Bax and Bak region, such as CytC (Zheng, et. al., 2004, Zalk, et. al., 2005, Kim et. al., 2023).

SP: Metabolic process Overview

The large family of sphingolipids, which play crucial roles in biomembrane that supply a variety of bioactive metabolites that control cellular activity, are the result of modifications to this fundamental structure. Sphingolipids come in a variety of shapes and functions, but same synthetic and catabolic channels regulate their creation and destruction. The category of lipids called GSL that has hundreds of several kinds of sphingolipid and differs in both the kind. These molecules may differ in the makeup of their acyl chains because they are also derived from ceramide precursors, adding even another level of variety. The two main groups of glycosphingolipids are glucosphingolipids and galactosphingolipids. The enzyme GCS, is initially responsible for the synthesis of glucosphingolipids. The enzyme GalCerS, which differs from GCS, produces galactosphingolipids (Liu, et. al., 2013). The variety in lipid binomial is multiplied by a factor of many thanks to the further division of glycosphingolipids based on additional modification by distinct glycosyltransferases. The SM binomial that are formed concurrently with GSL, are far more prevalent, but they are distinguished by the presence of a phosphocholine head group. Although all SM binomial can also have different fatty acid chains connected to their alpha-amino group since they are made from a range of ceramide species (Manni, et. al., 2018). It is yet unknown whether the various fatty acid chain lengths in Sphingomyelins determine discrete roles or significant biophysical differences.

Sphingoloipid-1-Phosphate

Sphingolipid-1-phosphate also known as lysosphingolipis, is a signalling sphingolipid. The cardiovascular and immunological systems both use the naturally occurring bioactive lipid molecule sphingosine-1-phosphate (S1P) as a first or second messenger. S1P can act as a signalling mediator during cell migration, differentiation, proliferation, and death via connecting with its receptors (Cartier,

et. al., 2019). Although numerous studies have recognised S1P's prominent function in bone regeneration, its function is less well-known than S1P's functions in the immune and cardiovascular systems (Zhang, et. al., 2020). Additionally, Sphingolipid-1-phosphate is thought to act as a link in bone growth & resorption, giving hope to people with bone disease.

Future of Sphingolipid-1-phosphate on osteoclasts and osteobullets

The skeletal system is a dynamic metabolic system that experiences degeneration and rejuvenation. While healthy individuals consistently preserve this loop, patients with bone disease have bone demineralization creation and bone reabsorption, which can result in either increased or decreased bone mass. Sphingolipid-1-phosphate has been shown to be crucial for bone metabolism. More significantly, S1P collaborates with RANKL to act as a mediator in the cross-talk in bone remodelling. The entire cycle of bone regeneration is therefore included in S1P's therapeutic value.

S1P's impact on osteoclasts

Following induction with Receptor Acivator of Nuclear Factor Kappa-B Ligand and M-CSF, monocytes merge to create multinucleated osteoclasts. These cells secrete cathepsin K (CTSK) and HCl, which cause the demineralization of the bone matrix (Chen, et. al., 2018) S1P has associated with the movement and development of osteoclastic cells, according to earlier research (Ishii, et. al., 2009). Numerous experimental studies have shown that S1P affects OCP mobilisation and recruitment (Ishii, et. al., 2013). Gi and Rac may be implicated in S1PR1-mediated chemoattraction, according to results from a mouse model treated with pertussis toxin, a Gi protein inhibitor. Contrary to what was previously believed, a high extracellular S1P concentration causes OCP chemorepulsion to be regulated predominantly by S1PR2. Numerous investigations have demonstrated that the S1PR2 is downstream of the G12/13/Rho signalling axis (Ishii, et. al., 2010). OCP chemoattraction is increased in the presence of S1PR2 abnormalities, suggesting a detrimental influence of S1PR2 signalling on S1PR1 function. Intriguingly, osteolysis was significantly reduced in vivo but not in vitro in S1PR2/ animals. (Bravo, et. al., 2022). This distinction suggests that S1PR2 might not be enough to attract osteoclast precursors on its own. According to theories on the processes of OCP chemotaxis, S1PR1 is triggered by S1P, internalises quickly in an environment with high S1P, and is transported back to the cell membrane in an environment with low S1P. S1PR2 is therefore repressed when OCPs are in the bone marrow and dominant when OCPs are moving through the circulation.

S1P indirectly contributes to OCP differentiation. Typically, S1P affects this process by controlling the expression of RANKL or the signalling route that lies downstream of it. In BMM cultures, the presence of SPHK1, which is in charge of producing S1P, significantly lowers osteoclastogenesis (Ryu, et. al., 2006) co-cultivation of bone marrow derived macrophages with osteoblasts resulted in enhanced RANKL expression(Kikuta, et. al., 2013), which was the opposite of the intended outcome (Matsuzaki, et. al., 2013). Additionally, increased RANKL expression causes a sharp rise in BMM differentiation.

S1P's impact on osteoblasts

Contrary to osteoclasts, mesenchymal stem cells (MSCs) are the source of osteoblasts. Osteoblasts release collagen & various chemicals ossification & production, that play a crucial role in new bone tissue formation. Osteoblast recruitment, differentiation, and proliferation are essential for bone formation since they are in charge of bone mineralization.S1P controls OBP mobilisation and recruitment similarly to OCPs through S1PR1/S1PR2 downstream signals. S1PR1 promotes the JAK/STAT signalling axis, which both increase MSC migration. OBP chemorepulsion is mediated by S1PR2, whereas S1PR1 controls OBP chemoattraction. Additional research has demonstrated the independence and lack of crosstalk between the FAK/PI3K/AKT and JAK/STAT signalling axes. S1P is essential for OBP differentiation in addition to osteoblast localization. Large amounts of S1PR1-3 are expressed in osteoblasticcells.During OBP differentiation, S1PR3 expression increases significantly. Furthermore when S1PR3 is knocked out, indicating that S1PR3 governs osteoblastogenesis. Smad 6/7 phosphorylation, which prevents BMP-Smad pathway activation & denotes homeostasis, was likewise brought about by RhoA (Higashi, et. al., 2016). S1P, on the other

hand, promotes the expression of S1PR1 and S1PR2, resulting in positive feedback control.S1PR1-3 promotes OBP differentiation overall through a network of regulatory signals. S1PR3 directly controls osteoblastogenesis in this network, but S1PR1/2's differential influence is weaker than S1PR3's.Osteoblast survival and proliferation are essential for osteogenesis because mature osteoblasts continue to go through mitosis. S1P enhances osteoblast growth and survival, according to numerous studies (Lampasso, et. al., 2001). Protein kinase C (PKC) was later revealed to be a downstream signal of S1PR1 due to research showing that S1P increases PKCs. Some scientists even believed that PKC and MAPK work together to exert PKC's proliferation-promoting effects (Hutami, et. al., 2017) (fig 3). The majority of calcium is contained in bones, and intracellular **Ca^{2+}** is crucial for osteometastasis. The knowledge of the role of **Ca^{2+}** in maintaining bone homeostasis is greatly enhanced by the discovery of calcium signalling cascade involvement in S1P calcium signalling cascade. In addition, osteoblasts were treated with a Gi inhibitor, wortmannin or LY294002, and a PKC inhibitor to ascertain signal which subsequent of Sphingosine-1-phosphate receptor affects osteoblast death. As predicted, the findings showed that PI3K and G protein signalling are S1P's downstream signals for anti-apoptotic actions in osteoblasts. There is still a considerable need for additional investigation into the function of Sphingosine-1-phosphate receptor in, and these studies will have significant therapeutic implications for bone-related illnesses. Despite the paucity of data, mechanical stress was found to increase SPHK1 and decrease SPP, SPL, and SPNS2 levels in osteocytes, hence stimulating S1P synthesis. The mechanism was the translation of force by the osteocyte network into a biological response, such as bone repair.

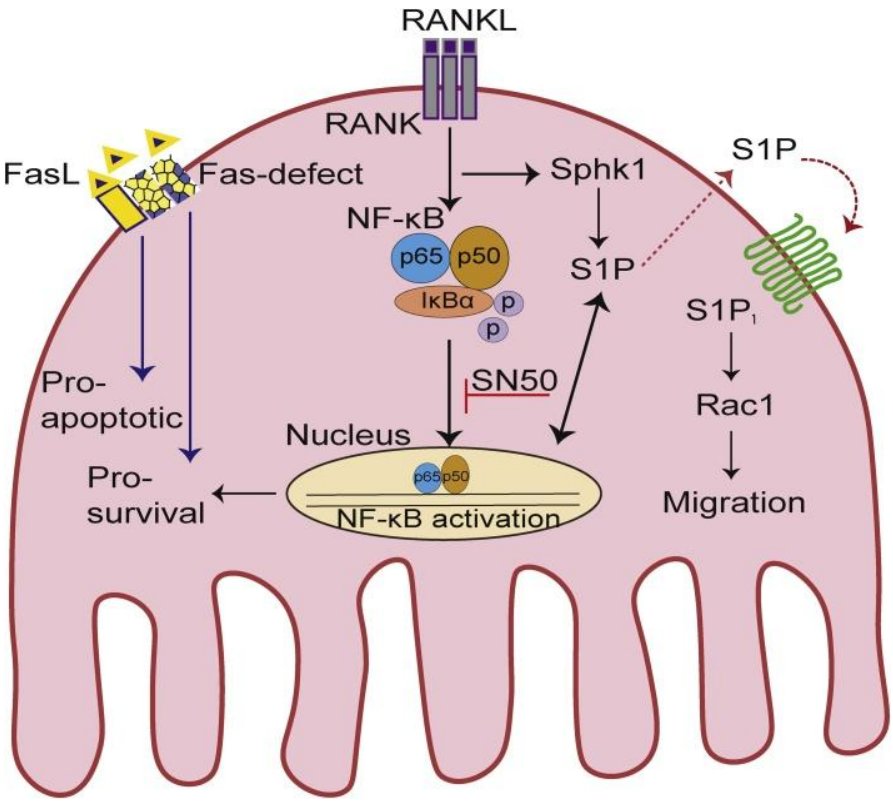

Fig 3: An envisioned model depicting how the interaction and influence between the Fas and S1P/S1P1 signaling patways regulate the process of osteogenesis. (adapted from Hutami, *et. al.,* 2017)

S1P's impact on how osteoblasts and osteoclasts communicate with one another

As already mentioned, S1P is essential for osteoclast and osteoblast differentiation, proliferation, and migration. The same S1PR (S1PR1/2) may influence osteoblast and osteoclast cell migration in the same way. The fact that osteoclasts & osteoblasts are not entirely hostile cells has also been gradually established. Instead, they work together and are closely connected to preserve equilibrium

and bone remodeling. Sphingolipid-1-phosphate is currently thought of a synergy that affects bone regrowth. Since osteoclasts are the principal source of S1P in the bone matrix, they may be crucial in controlling osteoblast migration, differentiation, and proliferation. Additionally, Sphingolipid-1-phosphate boosts RANKL expression in osteoblasts, which encourages osteoclast development and regulates osteolysis. Sphingolipid-1-phosphate promotes the balance of osteolysis and osteogenesis by acting as a coupling factor between osteoclasts and osteoblast (Kono, et. al., 2007). It is possible to significantly disrupt osteoclastogenesis without compromising bone turnover by decreasing S1P release from osteoclasts while raising S1P production in osteoclasts. Even though significant research has already been done in this area, further research is still urgently needed.

Lysophospholipid

Lysophospholipids are created by metabolic processes and disruption of cell membranes, with LPA and S1P serving as examples. Both compounds are recognised extracellular lipid mediators that communicate with vertebrates through unique G protein-coupled receptors. All organ system development, physiological operations, and pathological processes are governed by this pervasive signalling axis. LPA and S1P have critical cellular stress responses signalling, according to current study. Additionally, we go through how S1P regulates group behaviour, apoptotic cell clearance, and cancer immunosurveillance. Lysophospholipid research advancements have resulted in new therapies for autoimmune diseases.

Lysophospholipid mediators: an introduction and history

The primary building block of cell membranes, phospholipids, typically have 2 lipid chains. Lysophospholipids are phospholipids that contain only one fatty acid, despite the fact that their concentrations in cells and tissues are substantially smaller than those of normal phospholipids. Lysophospholipids are categorised, like phospholipids, according to the structure of their polar heads. For instance, lysophosphatidylcholine (LPC) and lysophosphatidylserine (LysoPS) both include L-serine in their polar heads. Lysophospholipids are alternatively categorised as glycerolysophospholipids or sphingolysophospholipids. The variety of molecular species that make up the lysophospholipids that have been found in vivo includes different polar group and acyl group combinations. Lysophospholipids, including lysophosphatidic acid (LPA), sphingosine 1-phosphate (S1P), lysophosphatidylinositol, and LysoPS, can cause cellular responses as well as a variety of pharmacological effects (Moolenaar, et. al., 2004). These lysophospholipids have been referred to as lysophospholipid mediators or bioactive lysophospholipids. Researchers need to determine the receptors, transporters, and metabolic enzymes that lysophospholipids interact with in order to understand their biological functions. Numerous of these important compounds have been found in the last 20 years. Additionally, research using knockout mice has demonstrated that lysophospholipids serve a number of pathological purposes (Kihara, et. al., 2014, Aikawa, et. al., 2015, Cartier, et. al., 2019). Additionally, we review new research on S1P and compare its pathobiology to that of LPA. The substance created by the reaction of PLs from egg ova & brain with enzymes from snake venom was historically known as lysophosphatide. Biochemists gave these substances the names lysolecithin and lysocephalin around the turn of the 20th century after observing their corresponding hemolytic and thromboplastic actions. Seymour Cohen, a renowned biochemist, and Erwin Chargaff (Sipos et. al., 2021) outlined the chemical makeup of lysophosphatides and proposed that lipid esterases are engage in synthesis of compounds containing fatty acids and a phosphoglycerol backbone.Lysophospholipids have come to be thought of as lytic substances implicated in cell death since they were chaotropic for membranes. But when administered in vivo, LPA affects systemic blood pressure and controls arterial ring contraction ex vivo (Tokumura, et. al., 1978). The GPCR the EDG-1, which was earlier identified as an inducible endothelium gene, was found to have a high affinity for S1P. S1PR1 was recognised as the original S1P receptor (Hla, and Maciag, 1990, Lee, et. al., 1998). In the end, four more S1PRs (S1PR2-5) were characterised as a result.

Lysophospholipid signalling: physicochemical considerations and general principles

To keep cells functioning at their best, the imbalance, structure, and transition of membrane phospholipids are effervescently controlled (Hishikawa, et. al., 2014). The organisation of membranes can be disturbed by cellular perturbations such as Ros heat changes (Holthuis and Menon, 2014, Kobayashi and Menon, 2018). As a result, animals have created sophisticated methods to return biological membranes to their homeostatic states. These methods depend on the functions of binding proteins, phospholipid transporters, and flippases.Lysophospholipids have distinct forms, solubility, and dynamic characteristics and are produced during membrane disturbance and homeostasis (Harayama and Shimizu, 2020). In general, esterases have no difficulty cleaving the two kinds of ester bonds—phosphodiester. Additionally, other phospholipases target these chemical bonds when they become active in disease situations, resulting in the production of lipid metabolites including eicosanoids and lysophospholipids. Lysophospholipids bearing ether linkages, or lysoplasmalogens, on the other hand, are more resistant to esterases. This article does not discuss the particular biology of lysoplasmalogens (Farooqui, et. al., 2001, Hossain, et. al., 2020). Lysophospholipids are less hydrophobic than diacyl phospholipids because they only contain one acyl chain. They can be freed from membranes and lipoproteins thanks to this characteristic. Thus, lysophospholipid synthesis is triggered by a variety of biophysical and metabolic triggers. Enzymes to quickly produce lysophospholipids are found in highly strong animal venoms and pathogenic bacteria (Zambelli, et. al., 2017). LPLs typically have a limited lifespan because they are quickly destroyed through dephosphorylation, acylation, or deacylation. LPLs are synthesised by certain pathways and have the same target G protein-linked receptors as eicosanoids (prostaglandins and leukotrienes) (Sheppe, et. al., 2021).

Pathological methods and lysophospholipids

Cellular Stress Signalling

The significance of lysophospholipids in membrane function is not well known, these lipids, which have distinctive physicochemical properties, very likely be the molecular foundation of membrane disturbances such swelling, blebbing, and endocytosis (Kano, et. al., 2022). Furthermore, certain compounds, like LPA and S1P, are easily soluble, which is made possible in part by lipoprotein particles and chaperone molecules that can stably attach to these molecules. Lysophospholipid molecules alter membrane characteristics and supply a reservoir of autacoids that have an effect on nearby cells that express GPCRs for those mediators (Cartier, et. al., 2019). These signalling pathways have a variety of biological impacts. Only vertebrates have been found to have lysophospholipid GPCRs, despite the fact that phospholipids are prevalent in membranes in all creatures. Therefore, it is likely that extracellular lysophospholipid GPCR signalling coevolved with vertebrates (Rosen, et. al., 2009, Kihara, et. al., 2014). The presence of many lysophospholipid GPCR types in the majority of cells suggests the extensive use of this signalling pathway in embryonic physiology and development. Different lysophospholipid GPCRs control downstream processes. Currently, it is unknown how lysophospholipid signalling affects the response to stress of cells with extended lifespans versus cells with fast cell turnover. In addition, nothing is known about how they affect cellular senescence and organismal ageing.

Conclusion

Multiple mechanisms explain how the metabolism of phospholipids and lysosphospholipids in the digestive tract increases the risk of cardiovascular and metabolic disease brought on by a high-fat diet. First off, phospholipid hydrolysis by PLA2g1b results in lysophospholipids like LPC, which cause hyperlipidemia, systemic inflammation, and cellular dysfunction even though it is not necessary for lipid absorption. Second, the conversion of unsaturatedLysophosphatidylcholine to unsaturated Lysophosphatidic acid by ATX results in the production of additional bioactive metabolites with pro-inflammatory characteristics that support cell dysregulation. Secondary messengers produced from lipids serve critical roles in signalling pathways that control cellular communication and different physiological activities. Diverse compounds called lipids have the potential to function as powerful signalling molecules, influencing cellular reactions to outside stimuli.

The phosphatidylinositol signalling pathway is one well-known example. PLC converts PIP2 into IP3 and diacylglycerol (DAG), which are both important components of these compounds. The release of calcium ions into the cytoplasm is then caused by IP3 binding to endoplasmic reticulum receptors, while DAG activates PKC, starting a series of phosphorylation processes. Numerous biological activities, including neurotransmission, cell differentiation, death and proliferation, are regulated by this system.

Arachidonic acid is a crucial lipid-derived secondary messenger that is released from membrane phospholipids by the enzyme phospholipase A2 (PLA2). Prostaglandins, leukotrienes, and thromboxanes are just a few of the bioactive lipids that are produced from arginine, which also functions as a precursor. These lipid mediators control vascular tone, immunological responses, inflammation, and platelet aggregation.

Sphingolipids, such as S1P, function as secondary messengers in signalling pathways. S1P interacts to particular GPCRs causing intracellular signalling processes that have an impact on immunological responses, cell migration, proliferation, and angiogenesis.

Additionally, recent studies have emphasised the function of messengers produced from lipids in controlling metabolic homeostasis, insulin signalling, and energy balance. Ceramides and diacylglycerols are lipids that can alter insulin sensitivity and aid in the emergence of metabolic diseases like obesity and type 2 diabetes.

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Conflict of Interest:

The authors declare no conflict of interest.

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