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# Inhibition Plcγ2 and Hydrophobic Acids Synthesis Cause Osteoarthritis, Diabetes and C-Lymphocytic Leukemia Diseases where Normally Plcs Can Recover Interferons Synthesis

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## Abstract

Proper S6K regulate BTK pathways wgich regulate PLCγ2 synthesis which are main regulations for thromboxane-A "TXA2" synthesis, and necessary for B-cell maturations and T-cells modulations and functions.

Deficiency in Ser amino acids and in hydrophobic amino acids are reflect decreasing in synthase enzyme lead to deficiency in BTK function and deficiency in PLCγ2 that lead increasing in colony stimulating Factor-1 "CSF-1 where PLCγ1 spesify to circuit to CSF-1 which upon synthase effect will promote PLCγ2 synthesis which necessary for activating BCRs for activating both IgM and IgD antigen for B-cells maturation and activities, for T-cells modulations, and for TXA2 synthesis.

Proper Akt, S6K1 synthesis, OPA1 enzymes and fatty Acyl-COAs are necessary for regulating RORs isoforms Biosynthesis which regulate both IFNs and PLCs synthesis {Where both IFNs and PLCs are covering each other IFNs <¬>PLCs} that PLCγ1 promote the PLCγ2 synthesis upon BTK regulations.

Osteoarthritis "OA" is characterized by a sharp expression in Gamma-Phospholipase C-1 "PLCγ1", with decreasing "or inhibition" in PLCγ2 which reflect decreasing in synthase functions and in IFN-beta synthesis that reflect decreasing or deficiency in TXA2 Biosynthesis.

The increasing in PLCγ1 with Deficiency in Ser amino acids will lead to deficiency in Ser phosphorylation signalling and deficiency in the pyrimidine kinases (PST-thymine and PS T-Cytosine kinases) synthesis , that lead to decreasing in synthase activity which will reflect down regulations in BTK pathways and inhibition in PLCγ2 productions which will reflect diabetes ( production of Androgen instead of estrogen), and can reflect Osteoarthritis"OA" prognosis which depend on the percentage of Deficiency or inhibition in basic amino acids and their basic necessary signaling pathways.

T2DM is strongly connected with OA diseases and are linked together by the deficiency in Ser amino acids and their phosphorylation, and any early decreasing in Ser and in hydroponic acids synthesis can lead to both and more disease. Pathogenic type 2 diabetes associated with progressive beta-cell impairment due to the mutations in the production of S6K1 (deficiency in Ser"TCT, TCC,TCA"), and inhibition in the PLCγ2 which due to inhibition or decreasing in Synthase and lead to deficiency in BCR activities. The releasing of PS/T-Thymine Kinases and PS/T-Cytosine kinases chains (mTORC1) from the phosphorylation oxydative process on Ser amino acids will lead to mutated S6K and Akt productions and decreasing or mutations in ATPase and GTPase which lead to decreasing in OPA1 repair and lead to synthesis of androgyne instead of estrogen which are depending on availability of hydrophobic amino acids synthesis including Ser and Tyr amino acids.

The effect of synthetase enzymes on biological molecules is for creating active gamma-subunits "PLCγ1" that can be modified by synthase effect for Beta-subunit synthesis "PLCγ2" then will be modified by phospholipase effects for alpha subunits productions. The releasing of pyrimidine kinases "PS/T-Thymine -Kinase and PS/T-Cytosine -kinase chains (mTORC1)" are so necessary steps for proper S6K productions and and for proper fatty Acyl-COAs synthesis which are necessary for regulating RORs Biosynthesis and for both IFNs and for PLCs production which started by productions of PLC-gamma and IFN gamma which are necessary for regulating proper PLCγ2 biosynthesis upon "BTK activity" then PLCγ2 are necessary for regulating BCR functions which imp for regulating both IgM and IgD activities for B-cell maturations , for adjusting anti-inflammatory processes and for T-cells modulations, then PLCγ2 is so necessary for thromboxane-A synthesis, and for bone growth and immune modulations. Deficiency in conversion of glutarate to glutamate and decreasing in proline (hydroponic acids) biosynthesis and availability can affect on cartilage synthesis and bone growth due to decreasing in stimulating mitochondrial OPA1 oxidations. It's imp to note that Tyrosine phosphatase

PTPs are important regulator of chondrogenic patterning and are critical regulators of tyrosine phosphorylation that it's activity depends on Tyr, Ser synthesis (hydrophobic acids) and on JAK state signaling activities. And so, the proline-rich tyrosine kinases regulate proper PLCs isoforms which compete for binding site at the very C terminus of fibroblast growth factor for osteorogenitor embryonic development, and bone growth.

Synthetase is the main regulator for PLCγ1 functions followed by synthase effects for active beta-subunits "PLCγ2" productions which can be able to "upregulate phospholipase abtivity" for alpha subunits (PLC-alpha) productions (alpha oxidations) for reactivating fibroblast growth factor receptor (FGFR2), for reactivating both IgM and IgD, and for TLR4 productions for osteoblast processes.

PLCγ1 can competes for a binding site at the very C terminus of FGFR2 for embryonic development and for bones growth, followed by synthase effect for PLCγ2 and for IFN-beta synthesis where both are necessary for activating BCR functions for B-cells maturation and for TXA2 synthesis.

PLCγ1 recruited to CSF-1 for two pathways activities 1st / re-activating IFNs productions which regulate MHC class1 and class-two for modulating cell-surface antigen protein functions , 2nd / re-activating PLCγ2 for modulating T-cells activities , where PLCγ1. Involved in the production of TRIM22 for mediating antiviral activities and anti-inflammatory processes through reactivating IFNs productions for PLCγ2 synthesis. PLCγ2 are so imp in anti-inflammatory processes (regulated by BTK functions) for thromboxane-A synthesis. Inhibitions or mutations in S6K, in BTK and then in PLCγ2 productions will cause an inherent or inhibition in CXCL12 then followed by inherent or inhibition in CXCR4 then reflect inherent or inhibition in the regulation of B-cell growth through mutations in IgM and in IgD.

Proline amino acids are necessary for reactivate OPA1 anabolic oxidations started by activating synthetase for producing gamma-subunits "PLCγ1" , then modulated by synthase effect for beta "PLCγ2" synthesis , and then modulated by phospholipase alpha oxidations for alpha-subunits "PLC-alpha" synthesis respectively for cartilage synthesis, for bone growth including antigen modulations (both IgM and IgD) and reactivation, and then for thromboxane-A synthesis.

**Keywords:** Phospholipase C-1 "PLCγ1", Phospholipase C-2 "PLCγ2 "necessary for anti-inflammatory steps, Osteoarthritis OA tissue cells, Osteoporosis tissue cells, Osteoclast processes, Osteoblast processes, Ser/Thr phosphorylation signaling, Deficiency in PS/-Thymine-kinases reflect mutated S6K, deficiency in PLCγ2, deficiency in B cells and T-cells modulation, and deficiency in OPA1 repair, S6K, estrogen, androgyne, JAK state signaling, _diabetes pathogenic tissue cells, Tyrosine phosphatase, PTPs, Colony-stimulating Factor-1 "CSF-1", inositol-1,4,5-triphosphate (IP3) and Diacylglycerol, thromboxane-A "TXA2", CXCR4, CXCL12, pathogenic chronic lymphocytic leukemia (CLL) tissue cells, B cells and B cells receptors "BCR", osteprogenitor pathway, Fibroblast growth factor receptor 2 "FGFR2", interferon regulatory factors (IRFs), antigen-specific immunoglobulin IgM and IgD.

## Introduction

Osteoarthritis is characterized by a sharp expression in Gamma-Phospholipase C-1 "PLCγ1", with decreasing in PLCγ2 "PLC beta" productions which can be improved by phospholipase oxidative processes for producing PLCγ2 and PLC-alpha which necessary for cellular proliferations, bone growth and calcium entry ", where PLCγ1 was highly expressed in human OA chondrocytes which are implicated processes including mitogenesis and calcium entry [1].

Phospholipase C isoforms (PLCs) are essential mediators for cellular signaling and for cellular metabolism. PLCs regulates multiple cellular processes including proliferations and biological bones growth by generating bioactive molecules such as inositol-1,4,5-triphosphate (IP3) and diacylglycerol.

That, PLCγ1 basis of inhibition-driven autophagy of IL-1β-treated chondrocyte confers cartilage protection against osteoarthritis [2]. PLCγ1 has the roles of analyzing biological molecules "Osteoclast" through expressing its own functions, while PLCγ2 has the role of functioning PLCγ1 through running beta-oxidations (regulated by synthase) for both anti-inflammatory processes and for promoting proliferations through activating phospholipase alpha-oxidation for activating PLC-alpha for proliferation and growth.

The slightly inhibition or decreasing in PLCγ1 will decrease osteoclast through decreasing analyzing process that will give priority for PLCγ2 synthesis "PLC-beta" regulated by synthase and its beta-oxidations for activating anti-inflammatory processes , and for promoting PLC-alpha production for proliferations functions. The increasing in PLCγ2 synthesis regulated by BTK will activate osteoblast processes, bone growth, cellular proliferation, and T-cells modulations".

The availability of Proline amino acids are necessary for stimulating and accelerating OPA1 oxidative processes which will activate cartilages synthesis through PLCγ2 synthesis, where the availability of hydrophobic amino acids synthesis "eg :Tyr, Leu, Pro, Gly, Ser, … etc" in vivo is important for creating gamma subunits synthesis upon synthetase effects.

Proline with necessary hydrophobic acids are necessary for and accelerating proper OPA1 oxidative processes which promote and activate necessary anabolic processes for cartilage synthesis through activating BTK pathways which regulate PLCγ2 synthesis for bone growth, and for modulating immune effectiveness.

The Deficiency in the conversion of glutarate to glutamate and decreasing in proline biosynthesis strongly effect on cartilage synthesis due to decreasing in the activation of mitochondrial OPA1 oxidative processes [3]. Deficiency in the mitochondrial OPA1 membrane repairs process can reflect deficiency in the proper S6K productions (which necessary for ATP and GTPase synthesis which necessary for mitochondrial OPA1 repair, that that will lead to decreasing in PLCs synthesis (decreasing in PLCγ2) then in SIRPα1, and in TLR4 biosynthesis, and can reflect increasing in catabolic analyzing processes (due to increasing in ATPase which depend on purines kinases production from Thr phosphorylation (PSTG-kinases and PSTA-kinases).

The decreasing in PS /T Thymine kinases and in PS/T-Cytosine kinases (pyrimidine kinases) productions due to decreasing in Ser and in hydrophobic acids synthesis including Tyr amino acids will lead to androgen production instead of estrogen (diabetes

disease), where the synthetase activities in diabetic diseases can be increased till will analyze phospholipids , foreign molecules and biological molecules (with decreasing or inhibition in pyrimidine kinases) lead to decreasing in the synthesis of anti-inflammatory tools eg PLCγ2 and IFN-beta productions.

Proper S6K1 synthesis promote ATPase and GTPase productions for OPA1 repair, for activating RORs pathways, for activating BTK pathways and for PLCγ2 productions, where all are depending on the purines and pyrimidine kinases productions through mTOR Ser/Thr phosphorylation pathways where necessary pyrimidine kinases are necessary for activating BTK and then for PLCs productions, for IFN synthesis, for proper MHCs synthesis, and for proper bone growth with T-cells modulations.

## Method and results

Proper S6K /BTK are so necessary for regulating PLCγ2 synthesis and are regulating proper thromboxane-A synthesis, B-cell maturations and T-cells modulations. Where, it's so important to Understand the main reasons that cause Osteoarthritis "OA" and diabetic diseases which are the deficiency of Ser amino acids and necessary hydroponic acids which lead to mutated S6K productions due to deficiency or inhibitions in Ser phosphorylation which normally is the basis of mTOR Ser /Thr phosphorylation Pathologies that are necessary for proper Akt, and S6K1 synthesis and then necessary for RORs and IFNs synthesis and also necessary for proper PLCγ2 productions.

Proper S6K productions through availability of Ser and Tyr amino acids are main regulator for ATPase synthesis and GTPase which necessary for OPA1 repair, and then for BTK pathways (which depends on Tyr a.a and on synthase effect for activating PLCγ2 ) and for proper PLCγ1 synthesis which are regulating PLCγ2 synthesis tool for necessary bone growth and cartilage synthesis.

Osteoarthritis "OA" is characterized by a sharp expression in Gamma-Phospholipase C-1 "PLCγ1", with decreasing "or inhibition" in BTK which lead to decreasing or inhibition in PLCγ2 "PLC beta" production that will lead to decreasing in beta-cells maturation, decreasing in cellular proliferation, and decreasing in T-cells modulations.

The increasing in PLCγ1 with Deficiency in Ser and Tyr will lead to mutated S6K productions , and decreasing in proper synthase activity and decreasing in BTK processes that will lead to inhibition in PLCγ2 synthesis and will reflect deficiency in Estrogen synthesis and increasing Androgyne synthesis that will give the Symptoms of diabetes and Osteoarthritis"OA" diseases. We'll discuss why both diseases are connected and are caused due to deficiency in Ser and in hydroponic amino acids, that availability of the Tyr and other hydroponic acids and their phosphorylation is necessary for BTK activities, and hydroponic amino acids synthesis depends on JAK signaling regulated by synthetase enzymes.

Deficiency in proper S6K, in Ser and in Tyrosine kinases "which regulated firstly by synthetase" will lead to increasing in PLCγ1 with decreasing in PLCγ2 synthesis (which Regulated by availability "pyrimidine kunases") will lead to Androgen synthesis instead of Estrogen which is Symptoms of "diabetes" and Osteoarthritis"OA" diseases :

PLCγ1 is a protein molecules that it's activity depending on Tyr phosphatase , and gamma common receptors synthesis which regulated by JAK STAT signaling, and also regulated by synthetase enzyme where synthetase is the main second enzyme in OPA1 chains after COX enzyme (followed by synthase and phospholipase respectively ) and necessary for hydroponic acids synthesis ) , that synthetase enzymes is so necessary for creating signals transmission which can reactivate mTOR Ser/Thr signaling pathway and for re-producing the active gamma-subunits which upon JAK signaling will produce their active receptors necessary for activating gamma subunits "PLCγ1" for beta-subunits "PLCγ2" synthesis upon synthase effect, then will produce alpha subunits "PLC-alpha" upon phospholipase effects for activating proliferations, and bones growth.

The PLCγ1/PLCγ2 double-deficient B cell progenitors have reduced expression of genes related to B cell lineage, IL-7 signaling, and cell cycle [4]. That the activities of both PLCγ1&2 are linked to each other and are so necessary for re-activating B-cells maturation , where, PLCγ2 regulate the productions of both antigen-specific immunoglobulin necessary IgM and IgD synthesis necessary for anti-inflammatory processes, and necessary for T-cells modulations, therefore the deficiency or mutations in PLCγ2 will lead to decreasing in or lead to Malignant transformation in B cells that can cause mutations or inhibition in IgM and in IgD synthesis and will lead to inhibition or mutations in TXA2 synthesis tool that can lead to a cancer problem as in chronic lymphocytic leukemia (CLL) disease and can cause several other pathogenic problems as diabetes and OA diseases.

B-cells are firstly promoted by the productions of both PLCγ1 which upon BTK which regulate PLCγ2 synthesis , and depend on proper S6K synthesis "that deficiency in Ser amino acids will reflect decreasing in the productions of the two types of pyrimidine kinases (PSTT-K and PSTC-k) that will lead to mutations in S6K synthesis (decreasing in thymine nucleotides contents) and lead to decreasing in Estrogen synthesis with increasing in Androgen synthesis which lead to pathogenic diabetes diseases [5].

Proper S6K , Estrogen, and PLCγ2 synthesis are depending firstly on availability of Ser amino acids and on the production of the two kinases (PSTTK and PSTCk) that are so necessary for reactivating the BTK pathways and reactivating the ribosomal ATPase which is necessary for repairing the mitochondrial OPA1 membrain (through regulating GTPase productions ), where proper OPA1 can be and BTK are necessary for "PLCγ2" synthesis which regulated by synthase effect for B-cell receptor synthesis for B-cells maturations, and then for anti-inflammation, then followed by creating PLC-alpha synthesis upon the upregulation of phospholipase functions for promoting proliferations and bone growth through SIRPa and TLR4 productions. In case of deficincy the mTOR Ser/Thr phosphorylations signalling due to deficiency in Ser phosphorylations and in Tyr kinases will lead to mutated S6K, deficiency in BTK activities, and deficiency in synthase functions that will lead to deficiency in PLCγ2 synthesis and will lead to androgyne productions with deficiency in Estrogen synthesis which will give the symptoms of diabetes and Osteoporosis pathogenic diseases , and also the deficiency in PLCγ2 or will lead to deficiency in TXA2 synthesis that can lead to cancer pathogenesis CLL diseases.

Pathogenic type 2 diabetes associated with progressive beta-cell impairment due to deficiency in Ser and Tyr kinases synthesis that will lead to deficiency in BTK functions and inhibitions or decreasing in PLCγ2 productions.

Tha availability of Ser, Tyr and necessary hydrophobic acids are necessary for re-activating BTK which necessary for promoting

PLCγ2 productions which is necessary for both B-cell maturation and for thromboxane-A2 "TXA2" synthesis, and also for bone growth [6A].

The inhibition in active beta subunits productions "PLCγ2" can be the reason of decreasing in the hyperpolarization and then electrical activity will lead to decreasing in the abolition of Ça+ which will lead to decreasing in blood pressure and Ça precipitations in blood vessels.

Also, the deficiency in Tyrosine amino acids will prevent the production of tyrosine phosphatase which needed for the synthesis of phospholipase C 2 that promote cellular proliferation including TXA2 synthesis , and then the reduction and deficiency in Tyr amino acids "hydrophobic acids" will reduce or inhibit Drutons tyrosine kinases "DTK" followed by reduction in PLCγ2 synthesis.

Now it is important to consider that proper S6K and Tyr kinases are the main regulator for PLCγ2 synthesis , and it has been reported that the phospholipase Cγ2 (PLCγ2) is activated from a variety of cell surface receptors such as SyK "S6K", and BTK which phosphorylate and activate PLCγ2 [6].

Proper S6K1 synthesis is the basis for ATPase, and GTPase synthesis and also is the basis for ribosome repair where, GTPase is necessary for G-protein synthesis, for OPA1 membrane repair, and for ribosomal repairs that always necessary for regulating cellular growth and anti-inflammatory Processes.

As the GTPase is a regulator tool for BH4 and NO 3 productions For synthase repair and activity, As, S6K1 is the main regulator for both PLCγ1 synthesis and then for PLCγ2 synthesis upon synthase functions which later will regulate the beta-cells maturation and survival upon productions of firstly CXCL12 then CXCR4 productions.

Also, it has been approved that T2DM is connected with OA diseases, where T2DM has a pathogenic effect on OA through 2 major pathways involving oxidative stress and low-grade chronic inflammation resulting from chronic hyperglycemia and insulin resistance [7].

Pathogenic type 2 diabetes associated with progressive beta-cell impairment due to the not normal production of insulin which due to deficiency of Ser phosphorylation and other necessary amino acids (mainly Ser, Tyr, Leu, Pro a.a.) that will lead to decreasing "or mutation" in the S6K productions, and will lead to Androgen production instead of Estrogen, and the cholesterol which depend on pyrimidine synthesis is the main substrates for Estrogen synthesis regulated by ROR anabolic pathways", that will lead to high ATPase productions (due to availability of purines with decreasing in pyrimidine synthesis) with deficiency estrogen synthesis , that also can activate IFN gamma, but with decreasing in IFN-beta, and alpha that can lead to increasing in "catabolic processes " with decreasing in the ROR pathways "anabolic process", and decreasing in proper PLCγ2 productions that will reflect Ca+ precipitations and arterial hypertension.

Where, it has been reported that insulin activates the K-ATP channels of pancreatic β-cells and islets, resulting in membrane hyperpolarization, and the abolition of [Ca2+]I oscillations [8].

And, the low abolition of [Ca2+]I oscillations in the case of T2DM indicates decreasing or inhibition in pyrimidine synthesis "which regulated by synthetase", also indicate decreasing in synthase functions, and decreasing in PLCγ2 synthesis "that has the role of modulating inositol 1,4,5-trisphosphate-mediated calcium oscillations for bone growth". Also, decreasing in membrane hyperpolarization can give reflection of decreasing in OPA1 synthase oxidations which reflect decreasing in membrane hyperpolarization due to decreasing in PLCγ2 synthesis and activities. (PLCγ1) can be reactivated by platelet-derived growth factor "GF" receptors, insulin-like GF 1 receptor (which reflect deficiency in proper cells and bones growth), but in brief PLCγ1 productions can produced and re-functioned by several active growth factor (GF) receptors through their feedback and by firstly stimulate synthetase for gamma subunits synthesis followed by synthase then phospholipase which can re-promote growth factor activities as epidermal GF receptor [EGFR], and platelet-derived GF receptor, where due to activating GFs processes which can re-increase hyperpolarization and functioning Ca+ throughout the synthesis of PLCs that will run the pathway of bone growth and modulate immune and cellular functions .

The main PLCγ1 proper activities is regulated firstly by main ribosomes and then by proper S6K productions from mTOR Ser / Thr phosphorylation pathways followed by JAK STAT signaling for producing the Tyr-phosphatase, gamma common receptors, and other necessary helical proteins receptors which adopt and reactivate PLCγ1&2 synthesis and activities for adopting anti-inflammatory, for B-cells maturation, for T-cells modulation, and for bone growth with proper cellular proliferation.

PLCγ1 is a necessary Protein regulated firstly by chromosomes which will transfer the necessary codon to ribosomes for creating their necessary ATPase for acting on mTOR Ser/Thr for S6K synthesis , and then for optimum OPA1 repair for reactivating OPA1 enzymes which will appear their function during stimulating RORS isoforms Biosynthesis which will begins by productions of gamma subunits which can be considered as PLCγ1 and IFN gamma where both are reactivating each other and then reactivate PLCγ2 productions, upon BTK functions which can renew Tyr amino acids and phosphatase functions where JAK signaling are mediated for creating and activating necessary receptors for active PLCγ2 synthesis which will promote active immune modulations, cellular proliferation, and bones growth including thromboxane-A 2 synthesis for renew blood cells.

Hydrophobic acids such as Tyrosine, Ser, proline are necessary for facilitate the OPA1 oxidative process and cellular activities including B-cells maturation and survival that can protect proliferations processes of bones developments (also can activate tumor growth in case of synthase or OPA1 dysfunction when lose or deprived of some necessary amino acids), where, proline is so necessary for activating OPA1 enzymes functions which activate bone cartilage growth , and activate BTK pathway which necessary for FGFR2 gene expression for bones developments .

Tyrosine amino acids increase alertness and bone development through activating tyrosine kinases and PLCγ2 productions, that Tyrosine phosphatases which are potential therapeutic targets for fighting bone disorders [9].

Protein tyrosine phosphatase (PTP) gamma (carry−ve charge regulated firstly by synthetase gamma-oxidations) has been proposed to be an important regulator of chondrogenic patterning, where PTPs are critical regulators "and renewer" of tyrosine phosphorylation at multiple stages of bone development and metabolism [10].

And, proline-rich tyrosine kinases regulate osteprogenitor cells

and bone formations, so Tyrosine and Proline (where their synthesis firstly regulated by synthetase in vivo) are regulating PIPs and are critical regulators for multiple stages in bone development started by cartilage synthesis [11].

Tyrosine, Ser and proline are essential hydrophobic acids that produced in vivo upon the effects of synthetase enzymes on nutrients-mTOR, and on inflammations molecules for running pyrimidine synthesis then for creating and improving (modulating) active Gamma-subunits for PLCγ1 synthesis through RORs pathway functions which modulated and regulate both PLCγ1 (active gamma subunits ) and PLCγ2 (active beta subunits) which regulated by BTK functions for modulating immune functions for increasing anti-inflammatory efficiency , then for modulating proliferation by "PLC-alpha" active alpha subunits productions which necessary for MHC class 2, for SIRPa1, for TLR4 synthesis (notice as mentioned previously that PLCs can recover IFNs synthesis and vice versa but each isoform can recover own related isoform which can begins from either interferons or from PLCs ) , and for B-cells maturation, for T-cells modulation,for bone growth,and for TXA2 synthesis.

Gamma-subunits firstly moderated by RORs isoforms Biosynthesis then can reactivated by JAK STAT signaling for producing their own active gamma subunits receptors (as Gamma-common and other helical proteins) which can be promoted by IFN gamma too for re-activating PLCγ1, PD-1, MHC-class-1 and class-2 , then PLCγ1 will promote PLCγ2 (upon BTK regulations) where the emphasizing of that is the importance of PLCs in strengthening immunity and modulating T-cells which are timed by interferons Biosynthesis.

So PLCγ2 can be promoted also by IFN beta for reactivating B-cell receptors for promoting antigens IgM and IgD biosynthesis , and also PLCγ2 can promote IFN-beta for MHC class-2 which promote the SIRPα1, TLR4, and PD-L1 productions respectively necessary for bone growth, cells developments and T-cells modulations.

PLCγ1 competes for binding site at very C terminus of FGFR2 for embryonic development and bones growth, where, PLCs promote IFNs synthesis, IgM, IgD and TLR4:

PLCγ1 competes for a binding site at C terminus of fibroblast growth factor receptor (FGFR2) (which plays an important role in bone growth, particularly during "embryonic development") and is sufficient to upregulate phospholipase activity [12].

Indicated to me that RORs Biosynthesis pathway are also so necessary for reactivating both PLCs isoforms and IFNs isoforms which are so necessary for PLCγ2 synthesis for B-cells maturation, for increasing immunity effectiveness, and for bone growth with cellular proliferation, where as i mentioned previously that both IFNs and PLCs can reactivate and recover each other in critical situations.

Where, S6K and and OPA1 enzymes regulate RORs Biosynthesis which regulate both PLCγ1 and IFN gamma productions (notice synthetase regulate firstly the pyrimidine synthesis for hydrophobic acid synthesis), that PLCγ1 will regulate the PLCγ2 synthesis through BTK and OPA1-synthase functions for active beta-subunits ("PLCγ2") productions which stimulate the upregulation of phospholipase "activity" for active alpha subunits (PLC-alpha) productions which can reactivate the production of fibroblast growth factor and their receptors (FGFR2) for proliferations ,for bone growth, for TXA2 synthesis, and for T-cells modulations.

There are strong relationships between PLCγ1&2 bio-function for the MHC class 1 and MHC class 2 which promote SIRPα1, TLR4, and PDL1 productions which are necessary for proliferation, and for blood cells modulation and recoveries.

Only Synthetase enzyme in OPA1 mitochondrial membrane are having the ability of hydrolysis biological molecules, inflammations and phospholipid membranes in vivo for producing active gamma-subunits , but normally followed by the effects of the 2nd enzyme in OPA1 which is synthase for moderate beta-subunits for producing PLCγ2 which will be moderated by phospholipase effects for PLC alpha production, but in case of deficiency in the synthase activities or in presence of mutated S6K the Osteoclast will be activated , but Osteoblast activity is characterized by proper availabilities of S6K, synthase activities, and PLCγ2 synthesis with IFN-beta synthesis for increasing immune effectiveness and promoting proliferation for bone growth including TXA2 Biosynthesis.

Where, Interferon beta 2/B-cell stimulatory factor type 2 shares identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute phase protein response in liver cells [13].

PLCs isoforms synthesis are involved in multiple stages in TLR4 and interferons regulatory factors (IRFs) synthesis [14]. Where it indicate that PLCs can recover IFNs (and vice versa) for IFN-gamma productions which promote MHC class 1 and MHC class-2 which promote SIRPα1 synthesis and TLR4 for proliferation and bone growth. So the involvement of PLCγ2 in TLR4 synthesis started by promoting IFN-beta productions for modulate anti-inflammatory effectiveness followed by proliferation processes , and PLCγ1 can promote IFN gamma activities (PLCγ1 <⟶> IFN gamma) which responsible for promoting MHCs class-1 and class two then SIRPα1, TLR4 and PDL1 productions for proliferation, bone growth and T cells modulations. Also the availability of proper S6K1 for PLCγ1 synthesis are so necessary for promoting both PLCγ2 and IFN-beta then for TLR4 upon phospholipase upregulation.

So, proper PLCγ1 can be considered as important regulator produced in vivo for activating IFN gamma and vice versa necessary for regulating to both PLCγ2 and IFN-beta upon BTK activity for adopting anti-inflammatory processes which will be upgraded and moderated by phospholipase activities for PLC-alpha, SIRPα1 TLR4 and and for PD-L1 productions.

Therefore, PLCγ1 regulate PLCγ2 production where both regulated by S6K and by BTK pathways then regulated by tyrosine phosphatase receptors and by phospho-tyrosine receptors "PTyr-R"
For activating PLCγ2 productions which then regulate PLC-alpha reproduction for bone growth, for B cells maturation, for T-cells modulations, and for cellular proliferation.

PLCγ2 are basically depend on JAK signaling for SH2B adaptor protein "which are a Tyr kinase receptor family" that necessary for BCR mediate B cells maturations [15]. phospho-tyrosine "PTyr" are necessary for PLCs isoforms synthesis , and for SHP1Src homology region 2 domain-containing phosphatase 1 for regulating PLCs productions , for stimulating IFNs productions, for adopting anti-inflammatory processes, and for proliferations, B-cells maturation, and T-cells modulations.

PLCγ1 is associated with numerous inflammatory diseases due to deficiency in synthase (which depend on availability of Ser and Tyr), that synthase promote PLCγ2 productions upon BTK regulations. In sever serious diseases the deficiency in hydrophobic acids including Ser phosphorylation and due to deficiency in proline and in Tyrosine amino acids that intracellular oxidations will be run and regulated by Cox activities and by productions of mutated PLCγ1 for acting firstly on infections on biological molecules.

PLCγ1 recruit to Colony-stimulating factor-1 "CSF-1" and followed by synthase regulation for producing PLCγ2 necessary for reactivating anti-inflammatory processing IFN-beta productions which re-activate PLC-γ2 via tyrosine kinase upstream:

The PLCγ1 has the specificity toward colony-stimulating factor receptor synthesis (CSF-1) signaling which expressed on the cell surface that can cause the cells to proliferate and differentiate into specific blood cells, and considered as a class III receptor tyrosine kinase that associated with Neuroinflammation, where PLCγ1 is recruited to the CSF-1 receptor following exposure to the cytokine [16]. PLCγ1 has a function for recruit to CSF-1 necessary for promoting PLCγ2 synthesis by the suppression through IFN-β synthesis for re-activating anti-inflammatory and then followed promoting proliferation through activating both IFN-alpha and PLC-alpha, SIRPα1,, TLR4 and then PD-L1 productions.

CSF-1 is a members of the IL-1 receptor family regulated by Gamma oxidation (synthetase effects) for PLCγ1 synthesis for promoting PLCγ2 production for re-promting IFN-beta productions for modulating anti-inflammatory efficiency. That, CSF1R-expressing cells may play an anti-inflammatory role or a cancer-suppressive role [17]. As PLCγ1 recruiting to CSF-1 for regulating PLCγ2 synthesis so CSF-1 play necessary role in anti-inflammatory processes which regulated firstly by mitochondrial OPA1 and by proper S6K production, and by PLCγ1 synthesis.

Also, Tripartite motif (TRIM) 22 plays an important role in interferons (IFNs)-mediated antiviral activity and the Induction of TRIM22 by IFN-γ Involves JAK and PC-PLC/PKC [18]. So, PLCs synthesis modulate and regulate Tripartite motif (TRIM) 22 too (which has antimicrobial activities) productions through activating IFNs production.

Also, IFN-γ activates PLC-γ2 via an upstream tyrosine kinase to induce activation of PKC-α [19]. That PLCγ2 regulated by PLCγ1 which can promote IFN-gamma production (through feedback) which has a variety of activities including PLCγ2 re-productions upon the necessity regulations of the upstream of tyrosine kinases for re-activating PKC-α.

PLCγ1 recruited to CSF-1 for two pathways activities 1st / re-activating IFNs productions which regulate MHC class1 and class two for modulating cell-surface protein activities, 2nd / activating PLCγ2 for modulating T-cells , where PLCγ1. Involved in the production of TRIM22 for mediating antiviral activities and anti-inflammatory processes through reactivating IFNs productions for PLCγ2 synthesis which modulate T-cells and activate bone growth with activating necessary proliferation. And also PLCγ1 promote IFN gamma which regulate MHC-class-I, MHC class-2 synthesis which promote, SIRPα1, TLR4, and PD-L1 synthesis. Note that the inhibitions of PLCγ2 productions with PLCγ1 productions will lead to Osteoclast, but the proper balance of both PLCγ1 and PLCγ2 productions will lead to osteoblast where PLCγ2 are connected to IFNs productions too.

Also, the Colony-stimulating factor-1 "CSF-1" requires PI3-kinase-mediated metabolism for proliferation [20]. PLCγ1 recruited to Colony-stimulating Factor 1 "CSF-1". Depending on mTOR-Ser /Thr phosphorylation for p13k and for proper S6K productions, where CSF-1 will be suppressed by IFN-beta synthesis and also by PLCγ2 synthesis (regulated by synthase) for modulating anti-inflammatory processes and for upregulation of phospholipase activities for proliferation processes and for bone growth including TXA2 synthesis.
Where, The inhibitions of of fatty acid synthase "FAS" activity by C75
Is resulted in down regulation of phospho-AKT [21].

The inhibition in synthase will reflect increasing in CSF-1 and down regulations in PLCγ2 and IFN-beta followed by decreasing in IFN-alpha and in PLCalpha production lead to decreasing in cellular proliferation and in TXA2 synthesis.

PLCγ2 synthesis activate Osteoblast but PLCγ1 production with inhibition in PLCγ2 will activate Osteoclast (OC) by inhibiting the inositol 1,4,5-trisphosphate- PLCγ1&2 synthesis are re-modulating variety of cellular pathways including IFNs isoforms and osteoclast (OC) differentiation.
Where, PLCγ2 productions is important to be in proper balance with PLCγ1 synthesis for running osteoblast and for inhibiting osteoclast, where the increasing in PLCγ1 productions with inhibition or decreasing in PLCγ2 synthesis will activate osteoclast (OC) by inhibiting or decreasing in re-modulating inositol 1,4,5-trisphosphate "which mediated calcium oscillations and the up-regulation of the nuclear transcription factor NFATc1" [22].

That, inositol 1,4,5-trisphosphate and diacylglycerol productions require phosphoinositide synthase (PIS) for modulating OC differentiation through regulating transient receptor potential (TRP) channels which requires hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP)
Resulting in the generation of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG).
OPA1 synthase is necessary for creating sphosphoinositide synthase (PIS) which will regulate PLCγ2 synthesis for upregulate phospholipase activity for PLC alpha production for proliferations and bone growth, Where, increasing in PLCγ1 "with reduction or inhibitions in PLCγ2 productions will activate osteoclast but the reactivating proper PLCγ2 synthesis will activate Osteoblast.

PLCγ2, independent of PLCγ1, was required for receptor activator of NF-κB ligand–induced osteoclastogenesis by differentially regulating nuclear factor of activated T cells c1 (NFATc1), proper PLCγ2 Pathway for modulating osteoclastogenesis [23]. Processes mediated by synthase effect for modulating T-cells for adopting anti-inflammations and cellular protection followed by upregulation of phospholipase functions for cellular proliferation, bones growth and TXA2 synthesis.

BTK regulate PLCγ2 which regulate both BCR and Thromboxane-A 2 synthesis, where, CLL disease due to full inhibition in PLCγ2: Phospholipase Cγ2 is Critical for Dectin-1 mediated Ca2+ Flux and Cytokine Production in Dendritic Cells [24]. PLCγ2 has a critical activity in dendritic cells, where is having a Critical function for Development of a Murine Model of Inflammatory Arthritis [25].

And, as PLCγ2 has a critical activity in dendritic cells for activating NF-κB ligand–induced osteoclastogenesis By differentially regulating nuclear factor-activated T cells c1 "NFATc1"

As PLCγ2 production modulate first the capacity of T-cells of dendritic cells. PLCγ2 is critical for B-cell receptor (BCR) for B cells maturation and functions, and PLCγ2 participates in TCR signal transduction and plays a role in T-cell selection [26]. It has been reported that Properdin and factor H production by human dendritic cells modulates their T-cell stimulatory [27]. Properdin is plasma glycoprotein that when activated by PLCγ1 (and synthetase) that will be modulated by changing the unnecessary purines to pyrimidines for rebuilding necessary Tyr, Ser, Pro, then will be directed to x chromosome for translations and purification for being build by identical necessary sequences for being contain identical six thrombospondin that will be ready to be regulated and modulated by PLCγ2 for TXA2 synthesis and for modulating T-cells which mediate cellular and bone growth.

The increasing in PLCγ1 productions with deficiency or mutation in S6K and thus in Properdin will inhibit PLCγ2 functions and will reflect decreasing in B cells maturation with decreasing or mutations in the thrombospondin lead to inhibition in TXA2 synthesis and can lead to autoinflammation and immune dysregulation (APLAID) which can cause rare monogenic autoinflammatory disease. That, The diverse pathologies associated with PLCγ2 are exemplified by distinct genetic variants, where inherited mutations at this locus cause PLCγ2-associated antibody deficiency and immune dysregulation [28]. Thrombine activation is highly reactivate intermediate the true fibrin monomer and it rapidly, and irreversibly [29]. That Thrombine is activated by PLCγ2 which intermediate fibrin monomer. Where, PLCγ2 involved with fibrin formation, where Bruton tyrosine kinase (Btk) activates PLCγ2 ,11,12 leading to thromboxane A2 (TXA2) synthesis [30]. So, proper PLCγ2 synthesis depend on PLCγ1 and on BTK activities where both are necessary for regulating PLCγ2 for regulating thromboxane-A 2 and fibrin for re-modulating immune and T cells activities. Also, the anti-platelets and anti-thrombotic effects of Fc are carried out through oppression of PLCγ2 and subsequent DAG-PKC-TXA2 and IP3-[Ca2+] [31].

The activation of PLCβ through Gq, which results in the formation of IP3 and diacyl glycerol, plays an important role in mediating αIIbβ3 activation [32]. So in brief the proper S6K, PLCγ1, and BTK necessary for regulating PLCγ2 productions which is necessary for B-cell maturation and T-cells modulations , and necessary for regulating thromboxane-A synthesis.

Chronic lymphocytic leukemia [CLL] reflect Inhibition in BTK and in PLCγ2 synthesis which reflect Inhibition or impaire in Thromboxane-A : Proline amino acids are required for Collagen synthesis where, Collagen binds to its receptors and activate both the PLCγ2-DAG-PKC and PI3 kinase/Akt-p38 MAPK cascades, where p38 MAPK can activate cPLA2, which catalyzes arachidonic acid (AA) release to produce thromboxane A2 (TxA 2 ) formation [33,34]. Bruton's tyrosine kinase "BTK" activates PLCγ 2 variants mediating ibrutinib resistance in human CLL [35].

BTK inhibitors [ibrutinib, CNX-774] significantly attenuated TPA-induced cell invasion and migration in MCF-7 cells and inhibit the activation of the phospholipase Cγ2/PKCβ signaling pathways [36]. BTK was initially shown to be defective in the primary immuno-deficiency X-linked a gamma-globulinemia (XLA) and is essential both for B cell development and function of mature [37].

So, both of Collagen synthesis and BTK are the main functions for re-activating PLCγ2 which catalyzes arachidonic acid (AA) release to produce thromboxane-A2 (TXA 2 ) formation ( note the inhibition or mutation in BTK and PLCγ2 will inhibit TXA2 synthesis and will cause Chronic lymphocytic leukemia), where both BTK and PLCγ2 are so necessary for B cells maturation and are critical for B-cell receptor (BCR), where, inhibition or reduction in BTK and in PLCγ2 will reflect Inhibition in B-cells maturation, inhibition in T-cells modulations, and inhibitions in TXA2 synthesis and will be the result of Chronic lymphocytic leukemia "CLL" disease. Vascular endothelial growth factor receptor (VEGFR) but not KIT, platelet-derived growth factor receptor (PDGFR) and FMS-like tyrosine kinase 3 (FLT3) are critical for CLL cell viability [38].

MTOR Ser Thr phosphorylation pathway regulate S6K production and promote VEGF activities for reproducing TXA2 (but through PLCγ2 regulations) in one pathway, and the other pathway is stimulating the PLCγ1 pruductions and promoting BTK activities for activating PLCγ2 productions which will reactivate the proper TXA2 synthesis and mediate the activities of VEGF for producing TXA2, for reactivating tropomyocin, and reactivating G-actin filaments activities. My note is, the synthesis of proper TXA2 in vivo are fully depending on PLCγ2 and consequently on S6K and BTK activities and functions, but only VEGF are not enough and not satisfied for TXA2 synthesis.

The proper S6K synthesis which will reactivate the PLCγ1 and DTK which will promote the PLCγ2 synthesis which I can consider it as the main necessary proper tools for TXA2 synthesis for blood synthesis, for bones maturations and for cells growth and then CLL cell viability.

So, PLCγ2 (which basically regulated by ribosomes, by S6K, and by PLCγ1) promote TXA2 synthesis which can stimulate and reactivate VEGF synthesis upon feedback for tropomyocin and for G-actin filaments reactivations for running full cellular Biosynthesis, for blood filtering in veins, and for cellular metabolism.

Chronic lymphocytic leukaemia (CLL) is a malignancy of CD5+ B cells that is characterized by the accumulation of small, mature-appearing lymphocytes in the blood, in bone marrow and in lymphoid tissues due to PLCγ2 inhibition may due to full mutated S6K production.

PLCγ2 synthesis occurred mainly in bone marrow where normal blood synthesis is regulated by skeletal tissue that is having orders from basic ribosomes, but mature CLL blood are activated and formed only by the activities of mTOR Ser/ Thr signaling which promote the VEGF, toropomyocin synthesis (where both cannot promote TXA2 synthesis without PLCγ2 availability) that both VEGF and toropomyocin are necessary for reactivate G-actin filaments and re purify blood in veins. So why VEGF +toropomycine is producing white mature cells?? VEGF cannot regulate directly the PLCγ2 synthesis and consequently can't regulate TXA2 synthesis but TXA2 synthesis cannot be done without PLCγ2 regulations. Where VEGF responsible for increasing the plasma long lived-plasma cells (LLPC), then the generation of antigen-specific antibody for Durable humoral immunity (which produced by non-proliferating bone marrow [39].

Old blood cells when passes through spleen will be broken to save iron which bind to PLCγ2 for regenerate new blood cells by PLCγ2 which extracted in spleen which are responsible for metals transportations and proliferation for new cells, but inhibition in PLCγ2 with increasing in the mutated S6K will inhibit TXA2 synthesis and will increase long lived plasma which increased by increasing in nutrients-mTOR signalling.
The B cell receptor (BCR) signaling pathway (which regulated by PLCγ2 synthesis and activities) has critical cell survival implications in B-cells malignancies, such as chronic lymphocytic leukemia (CLL). Small molecule tyrosine kinase inhibitors of members of the BCR signaling pathway have proven to be transformational in treatment of CLL [40].

The B-cell receptor (BCR) is a key survival molecule for normal B cells and for most B-cell malignancies. In CLL, engagement of the BCR (which regulated by PLCγ2) by antigen occurs in vivo, leading to down-regulated expression and to an unanticipated modulation of glycosylation of surface IgM, [41]. So inhibition in PLCγ2 synthesis will inhibit BCR signalling function that will lead to inhibition in modulation in IgM which normally done by BCR function for activating B-cells maturation.

The anti-apoptotic cell IgM natural antibodies can regulate inflammatory responses through ancient pathways of the innate immune system that first arose long before the initial emergence of the adaptive immune system [42].

My note,
PLCγ2 first regulate BCR activities which regulate both of IgM & IgD synthesis through synthase enzyme regulations, where IgM is more activé and less stable than IgD, that IgM necessary for modulating and regulating inflammatory immune response and anti-inflammatory processes through modulating T-cells reactivities.

## Results and Conclusion

Chronic lymphocytic leukemia [CLL] due to Inhibition in PLCγ2 synthesis “due to inhibition in OPA1 synthase” lead to inhibition in CXCR12 where CXCR12 is the main activator and regulator for CXCR4 synthesis Upton phospholipase effects on CXCR12. Also inhibition in PLCγ2 Bio-Synthesis will reflect Inhibition in thromboxane-A2 production that TXA2 mainly regulated by PLCγ2 but not regulated by VEGF, where VEGF regulate white mature cells, and regulate Tropomyocin Activity.

Osteoarthritis “OA” is characterized by a sharp expression in Gamma-Phospholipase C-1 “PLCγ1” (which catabolize inflammations), with decreasing “or inhibition” in PLCγ2 “PLC beta” productions (which necessary for immune modulation, for B-cell maturation and for T-cells modulation and regulate TXA2 synthesis). The increasing in PLCγ1 with Deficiency in Ser amino acids , and deficiency in proper S6K, with decreasing or inhibition in OPA1-synthase activity will lead to inhibition in PLCγ2 which lead to diabetes and early Osteoarthritis”OA” prognosis.

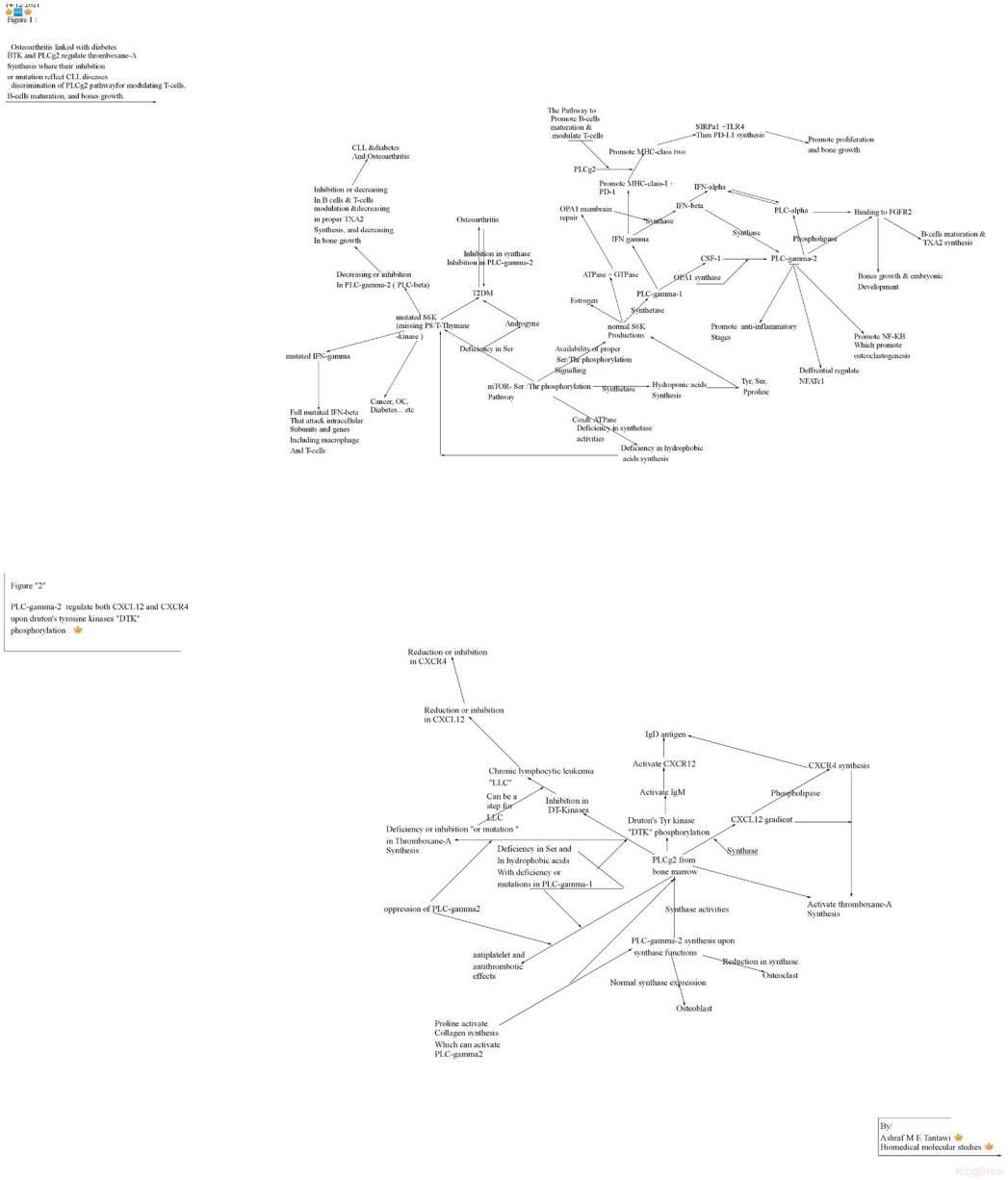
PLCγ2 are so necessary for re-modulating T-cells and immune efficiencies, and necessary for regulating antigen and thromboxane-A synthesis. The inhibitions or reduction or mutations in BTK and in its main proper PLCγ2 producions will cause an inherent inhibition or reduction in CXCL12 then will be followed by inhibition or reduction in CXCR4 then will lead to inhibition in the regulation of B-cell maturation , migration, adhesion, and also lead to severe decreasiing in anti-inflammatory processes of immune productive efficiency. Also inhibition in BTK and PLCγ2 mainly will reflect Inhibition in the two antigens IgM in and IgD synthesis.

Inhibition in synthase will reflect increasing in CSF-1 and down regulations in PLCγ2 and IFN-beta followed by decreasing in IFN-alpha and in PLCalpha production lead to decreasing in cellular proliferation and in TXA2 synthesis. Chronic lymphocytic leukemia “CLL” reflect decreasing or inhibition in growth-promoting signaling via the B-cell receptor. The Bruton tyrosine kinase (BTK) is the important for PLCγ2 synthesis which is necessary for B-cell maturations, T-cells modulation, and TXA2 synthesis. Bruton tyrosine kinase (Btk) necessary for activating PLCγ2,11,12 which necessary to activating thromboxane A2 synthesis, And necessary for modulating immune activities and T-cells.

Both Collagen and BTK pathways are necessary tools for re-activating PLCγ2 which catalyzes arachidonic acid (AA) release to produce thromboxane-A2 (TXA 2 ) synthesis , and necessary for B cells maturation and critical for B-cell receptor (BCR), where, inhibition in BTK and in PLCγ2 will reflect diabetes, Osteoarthritis, and the Chronic lymphocytic leukemia “CLL” disease depending on the percentage of Ser & hydroponic amino acids shortage and depending on the percentage of inhibition of necessary pathways needed for PLCγ2 synthesis and reactivities.

Also, inhibition in the availability of Ser, Tyr, Leu, Pro will reflect dysfunction in BTK function and inhibition in PLCγ2 synthesis that will lead to Osteosarcoma which is a cancer cases that produces immature bone (due to mutins in PLCγ2 and in TLR4 productions) found at the end of long bones (the tissue that carry the function of PLCγ2 synthesis), often around the knee.

The Deficiency in proline with inhibition in Ser, Tyr, leu (or mutations in synthase) will reflect Inhibition in synthase functions that will inhibit beta-subunits PLCγ2 synthesis and will lead to inhibition in TXA2 synthesis, that can reflect Inhibition in two or more of Interferon isoforms but will sure will reflect Inhibition in IFN-beta synthesis which promoted by synthase functions and by PLCγ2, that will reflect also decreasing or inhibition in MHC class-2 (which regulated by synthase and IFN-beta) that will lead to deficiency or inhibition in “SIRPα1, in TLR4, and in PD-L1 synthesis lead to isolations to that tissue part (due to calcium precipitation) that can lead to mutated immature bone synthesis and decreasing or inhibition in TXA2 synthesis.







## Porpoise of study,

Understanding that the inhibition or mutation in S6K and in hydroponic acids ( Ser, Tyr, Pro… ), in BTK and in PLCγ1 will lead to inhibition in PLCγ2 and in Thromboxane-A 2 then will be the main reasons for chronic lymphocytic leukemia "CLL" disease, where proper S6K /BTK and PLCγ2 are main regulations for thromboxane-A synthesis and necessary for B-cells maturations and T-cells modulations.

Also, it's important to Understand main factors that cause and link the Osteoarthritis "OA" with diabetes which are the deficiency in Ser (hydrophobic) amino acids and the mutated S6K productions lead to deficiency or inhibition in Ser phosphorylation signaling which normally is the basis of Ser/Thr phosphorylation signalling which necessarily for Akt, for S6K1 synthesis and necessary for RORs and IFNs synthesis, and also necessary for proper PLCγ2 productions , where S6K is the main regulator for ATPase, for ribosomes, for OPA1 repair, and for proper PLCγ2 synthesis , that I have to note that the percentage of the shortages ratio of amino acids or in the increasing in positive linkages are the main ratio that can define the degree and type of specific disease which can differ from other diseases or can linked with the same Syndromes of other diseases. , That also the shortage ratio between the beta Cytokines productions and the ratio of sudden high inflammations productions "and the type of its inflammatory molecules" have to be calculated and considered related to the patients ages (whether child, youth or old ages) and the duration of the chronic disease disease , that some can be confused to differentiate between auto-immune disease and regular disease problems diagnosis.

That, there was a case of a child with 9-year-old who had a suspicion of loose of bone maturation and growth, and has a sudden infection in the right lung and a lack of breathing with pain. It was found that there was a pulmonary abscesses in right lung, and there was a development with the appearance of an air bag or "inflammatory fluid bag" surrounding respiratory cells in right side.

The occurrence of sudden inflammations molecules and their growth was rapid enough faster than IFNs productions and faster than PLCγ2 productions due to to the age of the child "Note some her regular treating doctors diagnosed her medical conditions as a type Autoimmune disease and she has weakened immunity due to sudden fast infection related to her young age".

## High lights

Bruton tyrosine kinase (Btk) necessary for activating PLCγ2,11,12 which necessary to activating thromboxane A2 synthesis,

And necessary for modulating immune activities and T-cells.

Both Collagen and BTK functions are necessary for regulating and re-activating PLCγ2 which catalyzes arachidonic acid (AA) to produce thromboxane-A2 (TXA2 ) synthesis , and the PLCγ2 are necessary and critical for B-cell receptor (BCR), where, inhibition in BTK and in PLCγ2 will reflect diabetes, Osteoarthritis, and the Chronic lymphocytic leukemia "CLL".

_proper healthy PLCγ2 are so necessary for increasing re-medulate immune efficiencies, and for re-modulate IgM and IgD antigen and T-cells functions , and also proper healthy PLCγ2 productions (which depend on PLCγ1 and BTK Biosynthesis) are so imp for recover osteoporosis and both Osteoarthritis and diabetes.

_inhibition in PLCγ2 Bio-Synthesis can reflect decreasing or inhibition in Thromboxane-A 2 synthesis that can lead to CLL diseases,

Where, CLL characterized by inhibition in BTK which regulate PLCγ2 synthesis in bones tissue near knee which the only responsible for TXA2 synthesis (neither VEGF nor Tropomyocine where both can activate only white plasma which characterized CLL diseases with inhibition in TXA2 synthesis ) .

_Chronic lymphocytic leukemia (CLL) observed during treatment with B-cell receptor inhibitors pathway including inhibitor of Bruton's tyrosine kinase-PLCγ2, where, CLL can be strongly linked to Osteoporosis "OA", and Linked to both Osteoarthritis and diabetes too.

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