

Osteoarthritis Linked to Diabetes Characterized Sharp Decreasing in Ser/Proline/Plcy2 with Increasing Plcy1, where Inhibiting S6K/BTK / Plcy2 Affect TXA2 Synthesis Cause C-Lymphocytic Leukemia

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ABSTRACT

Proper S6K /BTK and PLC γ 2 are main regulations for thromboxane-A synthesis, and necessary for B-cell maturations and T-cells modulations and functions. The main factors that cause the Osteoarthritis "OA" and diabetes and linked between them are the deficiency of Ser amino acids and decreasing or down regulations of Ser phosphorylation signalling pathway which necessary for proper S6K productions, where normally the Ser phosphorylation signalling pathway is the basis of Ser /Thr phosphorylation signalling which normally necessary for proper Akt, S6K1 synthesis and necessary for RORs and IFNs synthesis and also necessary for running proper BTK and proper PLC γ 2 productions , where S6K is main regulator for ATPase and for proper PLC γ 1 and for PLC γ 2 synthesis which necessary for bone growth and for increasing and modulating immune efficiency. Osteoarthritis "OA" is characterized by a sharp expression in Gamma-Phospholipase C-1 "PLC γ 1", with decreasing "or inhibition" in PLC γ 2 "PLC beta" productions. The increasing in PLC γ 1 with Deficiency in Ser amino acids will lead to deficiency in Ser phosphorylation signaling (which is main basis for Ser/Thr phosphorylation signalling which has the main function of producing proper S6K) , and decreasing in synthase activity will reflect down regulations in BTK pathways and lead to inhibition in PLC γ 2 production which will reflect diabetes (inhibition in Estrogen with the production of Androgen instead of estrogen) and can reflect early Osteoarthritis "OA" prognosis dépend on the percentage of Deficiency or inhibition in basic amino acids and in basic necessary signaling pathways. The proper S6K are so necessary for reactivating both PLC γ 1&2, where phospholipase C γ 2 (PLC γ 2) is activated from a variety of cell surface receptors such as SyK "S6K". As, the B cells are promoted by the function and activities of both PLC γ 1&2, as the deficiency in Ser amino acids will reflect decreasing in Ser phosphorylation pathways and then decreasing in Estrogen synthesis, with increasing in Androgen synthesis which lead to decreasing in PLCs isoforms production and lead to pathogenic diabetes problem. So T2DM is strongly connected with OA disease, and both are having the same syndrome of causing their pathogenic problems, and any early step from any of those two or more similar diseases can lead to the other. Pathogenic type 2 diabetes associated with progressive beta-cell impairment due to the mutations in the production of normal insulin which due to missing of Ser phosphorylation signaling during mTOR Ser/Thr phosphorylation pathways that reflect Inhibition in the releasing of PS/T-Thymine -Kinase and PS/T-Cytosine -kinase chains (mTORC1) which are regulating hydrophobic amino acids synthesis which can be modified by synthetase enzymes for creating the first active gamma-subunits (upon synthetase effects) that will be modified by synthase effect for Beta-subunit synthesis then for alpha subunits upon phospholipase effects respectively. The previous of the releasing of PS/T-Thymine -Kinase and PS/T-Cytosine -kinase chains (mTORC1) from specifically the phosphorylation of Ser pathway is so necessary steps and mechanism for normal S6K productions, necessary for IFN-Gamma and for PLC γ 1 productions, and therefore necessary for normal PLC γ 2 synthesis which is necessary for B-cell activities, for T-cells modulations, for modulating anti-inflammatory steps and procedures, for thromboxane-A synthesis, and for bone growth and modulation. Inhibition in PS/T-Thymine -Kinase and PS/T-Cytosine -kinase chains (mTORC1) productions can be the main reason for inhibition the beta subunits productions that can be the reason of decreasing in the hyperpolarization and then electrical activity will lead to decreasing in the abolition of Ca^{+} which

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will lead to increasing in the dropping in blood pressure. Deficiency in conversion of glutarate to glutamate and decreasing in proline biosynthesis can affect on cartilage synthesis and bone growth due to decreasing in the activities of mitochondrial OPA1 oxidations. PTPs (Tyrosine Phosphatase) are important regulator of chondrogenic patterning and are critical regulators of tyrosine phosphorylation that its 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 osteoprogenitor embryonic development, and bone formations. Synthetase is the main regulator for PLC γ 1 activities followed by synthase effects for beta-subunits ("PLC γ 2") productions which is able to "upregulate phospholipase activity" for alpha subunits (PLC-alpha) productions for reactivating fibroblast growth factor receptor (FGFR2) and for reactivating antigens and TLR4 productions. Where, PLC γ 1 competes for a binding site at the very C terminus of FGFR2 for embryonic development and bones growth, where PLCs isoforms are involved in multiple stages in TLR4, interferon, and in anti-inflammatory steps. And also, PLC γ 1 recruit to CSF-1 is following imp stages for producing PLC γ 2 which is necessary for activating anti-inflammatory where, IFN- γ activates PLC- γ 2 via an upstream of tyrosine kinase.

The PLC γ 1 and PLC γ 2 (PLCs) are so imp in anti-inflammatory processes and can be considered as having the main roles of characterizing the activities of thromboxane and fibrin through re-modulating immune and T cells activities. Inhibitions or reduction or mutations in S6K, in BTK and in the original main normal PLC γ 2 production 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, migrations, adhesions and functions. Proline amino acids is necessary for reactivate OPA1 anabolic oxidations (started by synthetase, then synthase, then phospholipase for producing gamma "PLC γ 1", then beta "PLC γ 2", then alpha "PLC-a" subunits respectively) for cartilage synthesis which promote PLC γ 2 synthesis necessary for bone growth including antigen and thromboxane-A synthesis.

KEYWORDS: Phospholipase C-1 "PLC γ 1"; Phospholipase C-2 "PLC γ 2" 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 PLC γ 2, 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; 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"; Osteoprogenitor pathway; Fibroblast growth factor receptor 2 "FGFR2"; Interferon regulatory factors (IRFs); 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"; Osteoprogenitor pathway; Fibroblast growth factor receptor 2 "FGFR2"; Interferon regulatory factors (IRFS)

ABBREVIATIONS: CLL: Chronic Lymphocytic Leukemia Tissue Cells; BCR: B Cells and B Cells Receptors; FGFR2: Fibroblast Growth Factor Receptor 2; IRFs: Interferon Regulatory Factors; IP3: Inositol-1,4,5-Triphosphate; TXA2: Thromboxane-A; PLC γ 1: Phospholipase C-1; PLC γ 2: Phospholipase C-2

INTRODUCTION

Osteoarthritis is characterized by a sharp expression in Gamma-Phospholipase C-1 "PLC γ 1", with decreasing in PLC γ 2 "PLC beta" which improved by phospholipase oxidations for producing PLC alpha for proliferations and calcium entry ", where PLC γ 1 was highly expressed in human OA chondrocytes [1]. Which are implicated processes including mitogenesis and calcium entry.

Phospholipase C isoforms (PLCs) are essential mediators for cellular signaling and 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, PLC γ 1 basis of inhibition-driven autophagy of IL-1 β -treated chondrocyte confers cartilage protection against osteoarthritis [2]. The only presence PLC γ 1 has the ability and roles of analyzing biological molecules "Osteoclast" for expressing its own specified functions so, slightly inhibition or decreasing in PLC γ 1 will decrease osteoclast and also refunctioning PLC γ 1 for reactivating the expression of PLC γ 2 which reduce the analyzing function of PLC γ 1 and then give the priority to PLC-beta "PLC γ 2" for beta-oxidations for activating anti-inflammatory processes , and for PLC-alpha production for proliferations functions which for activating osteoblast processes, bone growth, and cells proliferations.

Where, the availability of proline is necessary for activating and accelerate OPA1 oxidative processes for cartilages synthesis and also the availability of necessary hydrophobic amino acids proper

synthesis "eg: Tyr, Leu, Pro, Gly, Ser, ... etc" will activate and will accelerate proper OPA1 oxidative processes which promote and activate necessary anabolic cycles for activating BTK which regulate PLC γ 2 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]. Also, deficiency in the mitochondrial OPA1 membrane bio-repairs can reflect deficiency in the proper S6K productions lead to deficiency in OPA1 mitochondrial repair synthetase activities lead to deficiency in OPA1 synthase, and in phospholipase activities and their molecular structure lead to decreasing in antigens synthesis and activities that can reflect decreasing in PLC γ 2 then in SIRP α 1, and in TLR4 biosynthesis, that can reflect increasing in catabolic analyzing processes that can analyze the phospholipid and interstatium fluid molecules.

METHOD AND RESULTS

S6K /BTK and PLC γ 2 are main regulations for thromboxane-A synthesis, and necessary for B-cell maturations and T-cells modulations. Where, it's important to Understand main factors that cause Osteoarthritis "OA" and diabetes which are the deficiency in Ser amino acids that lead to mutated S6K production due to deficiency or inhibition in Ser phosphorylation signaling which normally is the basis of Ser /Thr phosphorylation signalling which normally necessary for proper Akt, S6K1 synthesis and necessary

for RORs and IFNs synthesis and also necessary for proper PLCγ2 productions.

Proper S6K productions are main regulator for ATPase, for OPA1 repair, and for BTK and proper PLCγ1 & PLCγ2 synthesis which

necessary for bone growth. Osteoarthritis “OA” is characterized by a sharp expression in Gamma-Phospholipase C-1 “PLCγ1”, with decreasing “or inhibition” in BTK and in PLCγ2 “PLC beta” lead to decreasing in beta-cells and in T-cells modulations (Figure 1).

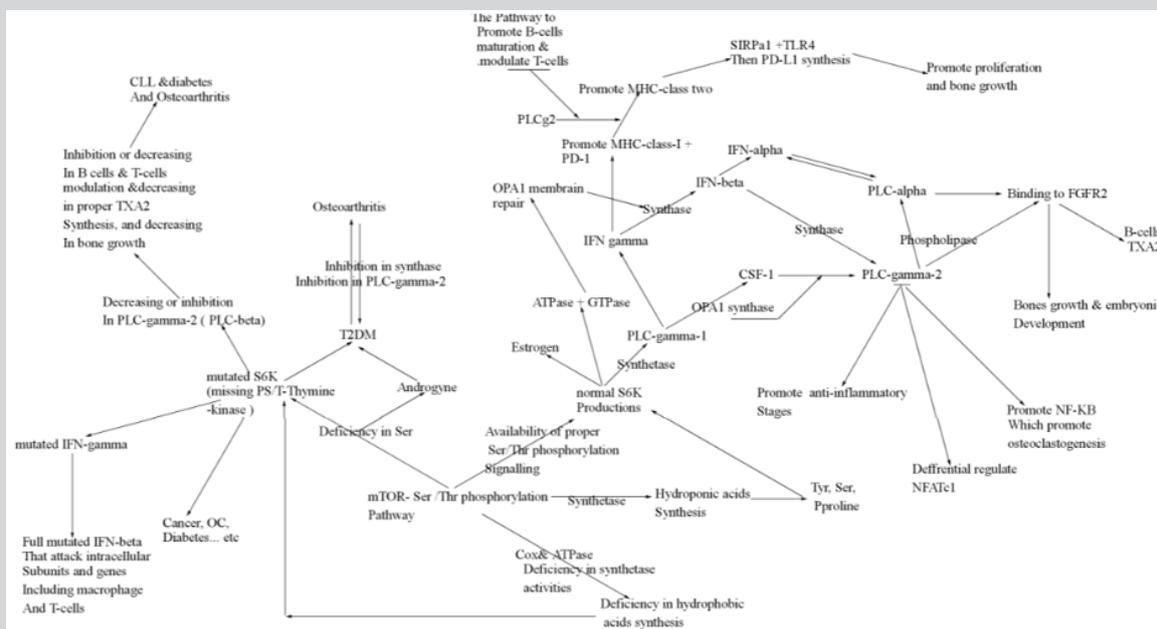


Figure 1: Osteoarthritis linked with diabetes BTK and PLCg2 regulate thromboxane-A Synthesis where their inhibition or mutation reflect CLL diseases. Discrimination of PLCg2 pathway for modulating T-cells, B-cells maturation, bones growth.

The increasing in PLCγ1 with Deficiency in Ser will reflect mutated S6K productivity, and in synthase activity with inhibition in PLCγ2 that will reflect Inhibition in estrogen synthesis and androgene synthesis that reflect diabetes problem and Osteoarthritis” OA that we’ll discuss why both diseases are connected, and their causes depend mainly on availability of Ser amino acids then on the Tyr and their phosphorylation signaling pathway.

Deficiency or inhibition in the proper S6K, in Ser and Tyr amino a. synthesis, will reflect increasing in PLCγ1 with decreasing in PLCγ2 and will reflect diabetes in Osteoarthritis “OA” diseases. Deficiency or inhibition in the proper S6K, in Ser and in Tyr amino a. synthesis in vivo “regulated by synthetase” will lead to increasing in PLCγ1 with decreasing in PLCγ2 synthesis and lead to diabetes and Osteoarthritis “OA” disease:

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 for gamma active subunits synthesis (or extraction) , that synthetase enzymes is so necessary for creating signals transmission which can reactivate mTOR pathway and for re-production the active gamma subunits which upon JAK signaling will produce active receptors necessary for activating beta-subunits synthesis which upon phospholipase will activate proliferation, 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-activation of B-cells maturation , where, PLCγ2 regulate the productions 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 PLCγ1&2 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 that will lead to cancers as chronic lymphocytic leukemia (CLL) and can cause several other pathogenic problems as diabetes and OA diseases.

B-cells are promoted by the productions of both PLCγ1 which upon BTK will regulate PLCγ2 synthesis, where PLCγ1 synthesis mainly depends on mTOR Ser /Thr phosphorylations signalling pathways (mTS/TP) and on S6K genes synthesis “that deficiency in Ser amino acids will reflect decreasing in the productions of the two types kinases PSTT-K and PSTC-k that will lead to mutations in S6K synthesis and lead to decreasing in Estrogen synthesis with increasing in Androgen synthesis which lead to pathogenic diabetes diseases [5].

Proper S6K synthesis is depending on availability of Ser amino acids and on the production of the two kinases PSTTK and PSTCk that are so necessary for reactivating ribosomal ATPase which is necessary for repairing the mitochondrial OPA1 membran (through regulating GTPase productions), where proper OPA1 is necessary for activates and regulating proper PLCγ1 productions and for “PLCγ2” synthesis upon synthase effect for B-cell receptor synthesis for B-cells maturation, and for anti-inflammation, then followed by creating PLC-alpha synthesis upon phospholipase functions for promoting proliferations and bone growth through SIRPa and TLR4 productions.

In case of deficiency in mTOR Ser/Thr phosphorylations signalling due to deficiency in Ser phosphorylation will produce non proper mutated S6K "missing Ser hydrophobic amino acids" that will lead to diabetes pathogenic problems, and will lead to inhibition in PLC γ 2 or will lead to mutated PLC γ 2 in some cases depending on the percentage of Deficiency of necessary hydroponic (Tyr, leu, Pro,... etc) that will lead to inhibition in Estrogen which is the substrate for RORs pathways and will lead to increasing in Androgyne instead of Estrogen that will inhibit PLC γ 2 synthesis and will lead to diabetes, and OA diseases, and can lead to cancer pathogenesis in the inhibition or mutation in TXA2 synthesis.

Pathogenic type 2 diabetes associated with progressive beta-cell impairment due to the mutations in the production of normal Estrogen which due to missing of Ser phosphorylation signaling during mTOR Ser/Thr phosphorylation pathways will lead to inhibition or decreasing.

The releasing of PS/T-Thymine -Kinase and PS/T-Cytosine -kinase chains (mTORC1) that those two kinases are depending on the availability of Ser and its phosphorylation pathway where Ser synthesis in vivo depending on synthetase which are regulate hydrophobic amino acids synthesis which can be modified by synthetase oxidations for creating the first active gamma-subunits that will be modified by synthase effect "beta-oxidation" for active Beta-subunit synthesis which necessary for "anti-inflammations" then for alpha subunits upon phospholipase effects "alpha-oxidations" which necessary for proliferation respectively.

The releasing of PS/T-Thymine -Kinase and PS/T-Cytosine -kinase chains or (mTORC1) from specifically the phosphorylations of Ser signalling pathway is so necessary steps for the mechanism of normal and proper S6K productions which necessary for IFN-Gamma and for PLC γ 1 productions, "in proper active forms" and therefore necessary for normal PLC γ 2 synthesis which is necessary for B-cell activities , for T-cells modulations, for modulating anti-inflammatory steps and processes, for thromboxane-A synthesis, and for bone growth and maturation [6].

The inhibition in PS/T-Thymine-Kinase and PS/T-Cytosine -kinase chains (mTORC1) productions will be the main reason for the inhibition of the beta subunits productions that can be the reason of decreasing in the hyperpolarization and then electrical activity will lead to decreasing in the abolition of Ca^{+} which will lead to decreasing in blood pressure.

Also, the deficiency in tyrosine amino acids will prevent the production of tyrosine phosphatase which needed for the synthesis of phospholipase C 1&2 that that promote cellular proliferation, and also reduction of and deficiency in Tyr amino acids "hydrophobic acids" will reduce or inhibit Drutons tyrosine kinases "DTK" (Figure 2). Now it is important to consider that proper S6K is the main regulator for PLCs isoforms synthesis which depend on S6K productions, and it has been reported that the phospholipase C γ 2 (PLC γ 2) is activated from a variety of cell surface receptors such as SyK "S6K", and BTK which phosphorylate and activate PLC γ 2 [7].

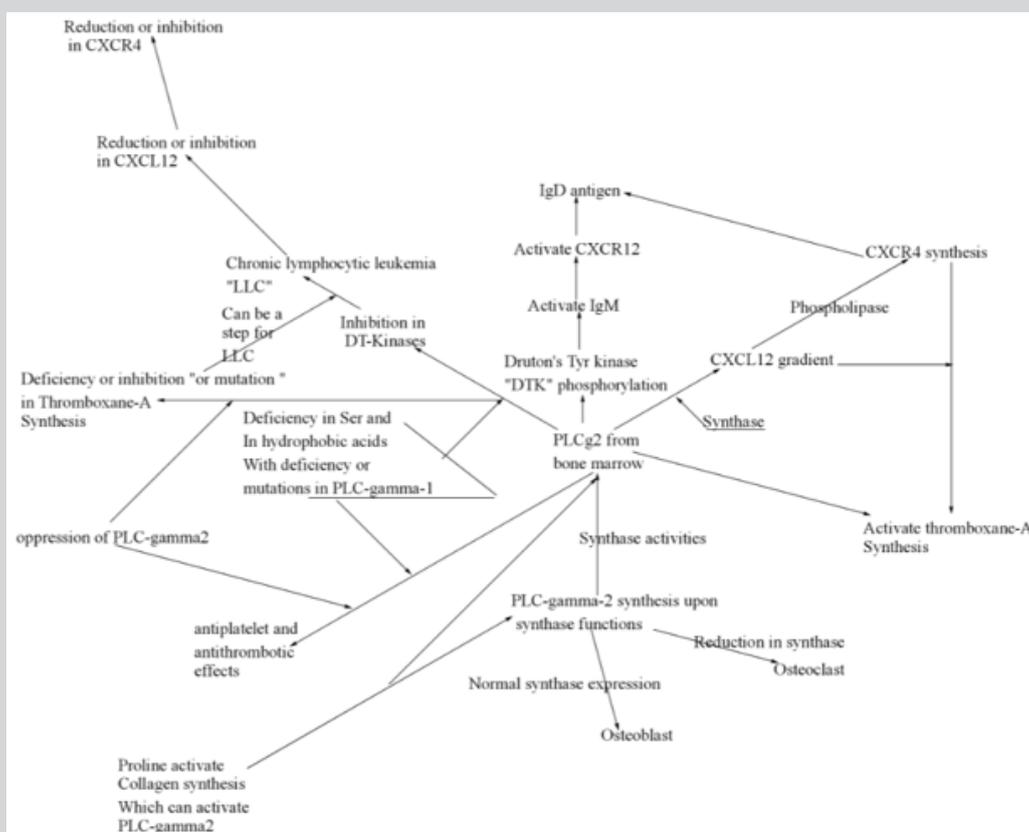


Figure 2: PLC γ 2 regulate both CXCL12 and CXCR4 upon druton's tyrosine kinases" DTK" Phosphorylation.

S6K1 is the basis for ATPase, and GTPase where, GTPase is necessary for G-protein synthesis, for OPA1 repair and re-modulations, and for ribosomal repairs and reactivations. 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 PLC γ 1 synthesis and then for PLC γ 2 synthesis upon synthase function which later will migrate for beta-cells survival upon production firstly CXCL12 then CXCR4 productions. Also, it has been

approved that T2DM is connected with OA, and both are having the same reason of causing their pathogenic disease, 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 [8]. 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 pathway during mTOR Ser/Thr phosphorylation pathways that will not produce normal S6K "due to deficiency in Ser and some other necessary amino acids (mainly Ser and Tyr, Leu, Pro a.a.) then will lead to decreasing "or mutation" in the S6K productions, that will lead to Androgen instead of Estrogen where Estrogen characterized by presence of Ser in their molecules, that will lead to high ATPase productions with deficiency estrogen which is the main substrat for RORs pathway that later will promote the IFN gamma, IFN-beta, and alpha that can lead to increasing in "catabolic effects" with decreasing in the ROR pathways "anabolic process" and decreasing in proper PLC γ 2 productions that 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 [9].

And, the low abolition of [Ca²⁺]_i oscillations in the case of T2DM indicates decreasing or inhibition in PLC γ 2 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.

(PLC γ 1) 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 PLC γ 1 productions can produced and re-functioned by several active growth factor (GF) receptors through feedback and by firstly reactivating synthetase followed by synthase then phospholipase which promote growth factor activities as epidermal GF receptor [EGFR], and platelet-derived GF receptor, where due to activating GFs processes it will be responsible for increasing hyperpolarization and functioning CA throughout the synthesis of PLCs that will responsible for running the pathway of bone growth and cellular biosynthesis processes.

The main PLC γ 1 proper activities is regulated firstly by proper S6K production 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 activate PLC γ 1&2 synthesis and activities for anti-inflammatory, for B-cells maturation, for T-cells modulation, and for bone growth and proper cellular proliferation.

PLC γ 1 is a necessary Protein regulated firstly by S6K which produced from mTOR Ser /Thr signaling pathway and regulated by OPA1 synthetase and then activated by JAK STAT signaling for both PLC γ 1 and then PLC γ 2 productions, where PLC γ 2 is also regulated by BTK for proper PLCs productions for cells proliferation and bones growth.

Hydrophobic acids such as Tyrosine, Ser, proline facilitate the survival and protect proliferation processes of bones development (also can activate tumor growth in case of specific synthase dysfunction when lose or deprived of some necessary amino acids) through facilitating OPA1 oxidative functions (especially when proline is available in OPA1 enzymes which activate their function)

and activate BTK pathways which necessary for FGFR2 gene expression for bones developments.

Where, Tyrosine amino acids increase alertness and bone development through activating tyrosine kinases, that Tyrosine phosphatases are potential therapeutic targets for fighting bone disorders [10]. 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 of tyrosine phosphorylation at multiple stages of bone development and metabolism [11].

And proline-rich tyrosine kinases regulate osteoprogenitor cells and bone formations [12]. so, Tyrosine and proline (where their synthesis firstly regulated by synthetase in vivo) are regulated by PIPs and are critical regulators of multiple stages in bone development.

Tyrosine, Ser, proline are essential hydrophobic acids that produced in vivo upon the effects of synthetase enzymes on nutrients, and on inflammations molecules for running pyrimidine synthesis and production for creating for improving Gamma-subunits then beta, then alpha subunits productions.

Gamma-subunits is then moderated by JAK STAT signaling for producing their own active gamma subunits receptors (as Gamma-common and other helical proteins) which promoted by IFN gamma for activating PLC γ 1, PD-1, MHC-class one and two antigens which promote the SIRP α 1, and TLR4 productions for bone growth and cells developments.

PLC γ 1 competes for a binding site at the very C terminus of FGFR2 for embryonic development and bones growth, where PLC isoforms are involved in multiple stages in TLR4, interferon, and in anti-inflammation.

PLC γ 1 competes for a binding site at the C terminus of fibroblast growth factor receptor (FGFR2) (which plays an important role in bone growth, particularly during development before birth "embryonic development") and is sufficient to upregulate phospholipase activity [13]. That, synthetase is the main regulator for PLC γ 1 activities followed by synthase effects for beta-subunits ("PLC γ 2") productions which is able to "upregulate phospholipase activity" for up regulate phospholipase activity for producing active alpha subunits (PLC-alpha) productions which responsible for reactivating fibroblast growth factor receptor (FGFR2) and for proliferation and bone growth, that it gives strong relationships to the reactivation and production of the MHC class two antigens which promote SIRP α 1 and TLR4 which are having the roles of proliferation, cells modulations and T-cells modulations.

Only Synthetase enzymes in OPA1 mitochondrial membrains are having the ability of hydrolysis biological molecules, inflammations and phospholipid membranes in vivo, therefore the active gamma subunits - (regulated by synthetase) in absence of beta subunits are able to analyze cells, inflammations and biological molecules (for producing prostaglandins), where beta subunits chain contains gamma and beta "upon beta oxidations" chain that during attacking inflammations or microbe in vivo the beta subunits will protect cells while only gamma subunits (in absence of beta subunits) will analyze biological molecules, but in availability of beta and alpha chains PLC γ 2 & PLC-alpha productions will have the roles of modulating and activating anti-inflammatory processes, B-cells maturation, T-cells modulations, and bone growth.

So PLC γ 1 is considered as active gamma chain containing necessary hydroponic amino acids that necessary for promoting and modifying the PLC γ 2 productions upon synthase effect that will modulate the increasing in anti-inflammations and modulating T-cells that can protect cells then will promote the PLC-alpha synthesis necessary for running proliferation and bone growth which also appears that strongly connected to promoting the activating of both SIRP-a and TLR4 productions which are having the same roles as PLC-alpha of running proliferation and bone growth.

Where, Some PLCs isoforms are involved in multiple stages in TLR4 and interferons regulatory factors (IRFs) synthesis [14]. Where it indicates the involvement of PLCs in the activating interferons regulatory tools (IFN-gamma, IFN-beta and IFN-alpha) which responsible for promoting MHCs "class one and two", SIRP α 1 and TLR4 where not SIRP α 1 and TLR4 are responsible for proliferation, bone growth and T-cells modulations. Also indicating that the availability of S6K1 and PLC γ 1 in proper molecular structure are so necessary for activating IFNs and for TLR4.

So, proper PLC γ 1 can be considered as important tools produced in vivo for activating IFNs necessary regulatory for anti-inflammations which regulate MHC class one and two and SIRP α 1 and TLR4 which are necessary for proliferation and T-cells modulations. The PLC γ 1 are produced upon OPA1 synthetase oxidative effects and activated by JAK signaling for gamma common, tyrosine Receptors, and other helical protein receptors productions which regulate PLCs isoforms activities and other genes biosynthesis "eg: antigen, PD-1, SIRP-gamma, and PLC γ 1 productions", that PLC γ 1 are containing so necessary regulatory basic amino acids for promoting antigen synthesis, for SIRP α 1, for TLR4 biosynthesis, and then for PD-L1 biosynthesis.

Therefore, PLC γ 1 are so imp for PLC γ 2 production which regulated by tyrosine phosphatase receptors and by phospho-tyrosine receptors "PTyr-R" for activating PLC γ 2 productions and then for PLC-alpha reproduction for bone growth, for B cells maturation, and for promoting anti-inflammatory steps through activating IFNs productions for regulating MHCs synthesis which necessary for SIRP α 1, TLR4, and PD-L1 productions where all are Contributing and activating the bone growth, proper anti-inflammations, T-cells modulations, and necessary cells maturation.

Where, are basically dependent on JAK signaling for SH2B adaptor protein "that are a Tyr kinase receptor family" which necessary for BCR mediate B cells maturation [15]. That, "PTyr" phospho-tyrosine "Which necessary for PLCs synthesis ", and for SHP1Src homology region 2 domain-containing phosphatase 1 synthesis are so imp for regulating PLCs synthesis, for reactivating IFNs and their pathways functions in anti-inflammatory processes including proliferation, B-cells maturation.

Notice that PLC γ 2 BCR mediate B-cell maturation which regulated by SH2B adaptor protein, so BTK is the so necessary regulatory factor for PLC γ 2 production for B-cell maturation and also for modulating T-cells.

PLC γ 1 is associated with numerous inflammatory diseases where firstly the productions of PLC γ 1 is for acting on infections for modulating the PLC γ 2 productions for running the PLC γ 2 pathways for firstly anti-inflammations followed by promoting PLC alpha for proliferation, that there are considerate limits % between the amount of inflammations from its inflammatory Source and the percentage of the productions of PLC γ 1, where in case of increasing

in the sudden inflammation related to PLC γ 1 productions will overcome in tissue lead to increasing inflammations but in case of providing the salvation through providing PLC γ 2 will reflect decreasing in inflammations with increasing in anti-inflammatory processes.

PLC γ 1 recruit to Colony-stimulating factor-1 "CSF-1" is following by imp stages for producing PLC γ 2 which is necessary for activating anti-inflammatory through activating, IFNs which activates PLC- γ 2 via an upstream of tyrosine kinase:

The PLC γ 1 has the specificity toward colony-stimulating factor receptor (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 PLC γ 1 is recruited to the CSF-1 receptor following exposure to the cytokine [16]. meaning of PLC γ 1 recruit to CSF-1 necessary for producing PLC γ 2 which is necessary for re-activating anti-inflammatory steps then follow the proliferation steps through activating SIRP α 1 and TLR4 and then PD-L1 productions.

So, CSF-1 is a member of the IL-1 receptor family which involved in completing anti-inflammatory cycles for proliferations is regulated by PLC γ 1 effect and regulations.

Where, CSF1R-expressing cells may play an anti-inflammatory role or a cancer-suppressive role [17]. As PLC γ 1 recruiting to CSF-1 for PLC γ 2 synthesis (where PLC γ 2 play imp role in anti-inflammations and modulating BCR and T-cells) so CSF-1 is playing necessary role in anti-inflammatory processes regulated firstly by OPA1 and then by PLC γ 1.

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 [17]. So, PLCs synthesis modulate and regulate Tripartite motif (TRIM) 22 (what has antimicrobial activities) productions through activating IFNs production.

Also, IFN- γ activates PLC- γ 2 via an upstream tyrosine kinase to induce activation of PKC- α [19]. As PLCs (sterted by PLC γ 1) activate IFNs productions which regulate PLC γ 2 productions, as proper PLC γ 1 is the first regulator for PLC γ 2 productions for bone growth and T-cells modulations.

So, PLC γ 1 recruited to CSF-1 for re-activating IFNs productions which regulate MHC class one and two for modulating cell-surface protein structure through activating PLC γ 2 for modulating T-cells, where PLC γ 1 involved in the production of TRIM22 for mediating antiviral activities and anti-inflammatory processes through reactivating IFNs productions for PLC γ 2 which modulate T-cells and activate bone growth with activating necessary proliferation through promoting PLC alpha, SIRP α 1, TLR4, and PD-L1 synthesis.

Note that the inhibitions of PLC γ 2 productions with continually PLC γ 1 productions will lead to osteoclast, but the proper balance of both PLC γ 1 and PLC γ 2 productions will lead to osteoblast where PLC γ 2 are depending on IFNs productions too.

Also, the Colony-stimulating factor-1 requires PI3-kinase-mediated metabolism for proliferation [20]. So, as PLC γ 1 recruited to Colony-stimulating Factor 1 "CSF-1" which involved in anti-inflammations and in proliferation as PLC γ 1 has own strong roles of activities for both anti-inflammations "upon circuit to recruited CSF-1", and for PLC γ 2 and PLC-alpha productions for running

proliferations including bone growth. The inhibitions of fatty acid synthase "FAS" activity by C75 is resulted in downregulation of phospho-AKT [21]. PLC γ 1 which regulated by both synthetase and by S6K productions are necessary for activating CSF-1 production which activate PLC γ 2 productions (upon synthase effect), but in the inhibition of synthase will reflect down regulations in p13k Akt and inhibition in PLC γ 2 productions. PLC γ 2 synthesis activate osteoblast but PLC γ 1 production with inhibition in PLC γ 2 will activate osteoclast (OC) by inhibiting re-modulating inositol 1,4,5-trisphosphate.

PLC γ 1&2 are modulating a variety of cellular pathways including osteoclast (OC) differentiation. Where, PLC γ 2 production is important for running osteoblast and inhibiting osteoclast, where the increasing in PLC γ 1 productions with inhibition in PLC γ 2 will activate osteoclast (OC) by inhibiting 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 production require phosphoinositide synthase (PIS) for modulating OC differentiation through regulating transient receptor potential (TRP) channels which need hydrolysis of equires hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP) resulting in the generation of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). So, OPA1 synthase is necessary for creating sphosphoinositide synthase (PIS) "regulated firstly by synthetase gamma-oxidations for activating firstly PLC γ 1 production followed by PLC γ 2 productions.

Both PLC γ 1 and sphosphoinositide synthase (PIS) are imp for promoting PLC γ 2 productions and necessary for proliferations and bone growth, Where, increasing in PLC γ 1 "with reduction or inhibitions in PLC γ 2 productions will activate osteoclast but the reactivating proper percentage of PLC γ 2 synthesis will activate osteoblast.

Where, PLC γ 2, independent of PLC γ 1, was required for receptor activator of NF- κ B ligand-induced osteoclastogenesis by differentially regulating nuclear factor of activated T cells c1 (NFATc1) [23]. That, JAK signaling are playing imp roles in running either osteoclast or osteoblast through mitochondrial OPA1 regulation activities, that high gamma receptors with decreasing in beta receptors will activate osteoclast but proper percentages of gamma and beta productions (proper% Between PLC γ 1 & PLC γ 2 productions) will activate proper osteoblast through activating PLC γ 2 production Which needed for TXA2 synthesis and for beta-cells maturation and activities.

PLC γ 2 can modulate immune activities and T-cells too, where Bruton tyrosine kinase (Btk) activates PLC γ 2 ,11,12 which activate thromboxane A2 re-synthesis. Phospholipase C γ 2 is Critical for Dectin-1-mediated Ca²⁺ Flux and Cytokine Production in Dendritic Cells [24]. PLC γ 2 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 PLC γ 2 has a critical activity in dendritic cells for activating NF- κ B ligand-induced osteoclastogenesis by differentially regulating nuclear factor-activated T cells c1 "NFATc1" As PLC γ 2 production modulate the capacity of T-cells of dendritic cells.

Where, PLC γ 2 is critical for B-cell receptor (BCR) for B cells maturation and functions, and PLC γ 2 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]. but I report that modulations of T-cells run by the functions of PLC γ 2 for re-activating NF- κ B by regulating NFATc1, while Properdin subunits composition can modulate NFATc1 or not.

The increasing in PLC γ 1 productions with deficiency or mutation in PLC γ 2 will reflect decreasing in B cells maturation and function and can lead to (APLAID) Autoinflammation and immune dysregulation which can cause rare monogenic autoinflammatory disease.

That, the diverse pathologies associated with PLC γ 2 are exemplified by distinct genetic variants, where inherited mutations at this locus cause PLC γ 2-associated antibody deficiency and immune dysregulation [28].

Thrombine activation is highly reactivate intermediate the true fibrin monomer and it rapidly, and irreversibly [29]. PLC γ 2 involved with fibrin formation, where Bruton tyrosine kinase (Btk) activates PLC γ 2 ,11,12 leading to thromboxane A2 (TXA2) synthesis [30]. So, PLC γ 2 synthesis can define the availability of the synthesis and activities of thromboxane-A and fibrin and re-modulating immune and T cells activities.

Also, the antiplatelet and antithrombotic effects of Fc are carried out through oppression of PLC γ 2 and subsequent DAG-PKC-TXA2 and IP3-[Ca²⁺] [31]. The activation of PLC β through Gq, which results in the formation of IP3 and diacyl glycerol, plays an important role in mediating α IIb β 3 activation [32].

So, in brief BTK necessary for PLC γ 2 productions which is necessary for B-cell maturation and functions, and also PLC γ 2 is so imp for thromboxane-A synthesis. Chronic lymphocytic leukemia [CLL] reflect Inhibition in BTK and then in PLC γ 2 synthesis which can reflect Inhibition or impair in Thromboxane-A Proline amino acids are required for Collagen synthesis [33]. Where, Collagen binds to its receptors and then activates both the PLC γ 2-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 (Tx A 2) formation [34].

Bruton's tyrosine kinase "BTK" activates PLC γ 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 inhibited the activation of the phospholipase C γ 2/PKC β signaling pathways. BTK was initially shown to be defective in the primary immunodeficiency X-linked agammaglobulinemia (XLA) and is essential both for B cell development and function of mature.

So, both of Collagen synthesis and BTK are the main functions for re-activating PLC γ 2 which catalyzes arachidonic acid (AA) release to produce thromboxane-A2 (TXA 2) formation (note the inhibition in BTK and PLC γ 2 will effect on TXA2 synthesis and will cause Chronic lymphocytic leukemia) and both BTK and PLC γ 2 are so necessary for B cells maturation and functions and are critical for B-cell receptor (BCR), where, inhibition or reduction in BTK and in PLC γ 2 will reflect the Chronic lymphocytic leukemia "CLL".

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 [37]. MTOR Ser Thr phosphorylation pathway regulate S6K production and promote VEGF activities for reproducing TXA2 (but through PLC γ 2 regulations) in one pathway, and the other pathway is

stimulating the PLC γ 1 productions and promoting BTK activities for activating PLC γ 2 productions which will reactivate the proper TXA2 synthesis and mediate the activities of VEGF for producing TXA2, for reactivating tropomyosin, and reactivating G-actin filaments activities.

My note is, the synthesis of proper TXA2 in vivo is fully depending on PLC γ 2 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 PLC γ 1 and DTK which will promote the PLC γ 2 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, PLC γ 2 (which basically regulated by ribosomes, by S6K, and by PLC γ 1) promote TXA2 synthesis which can stimulate and reactivate VEGF synthesis upon feedback for tropomyosin 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 PLC γ 2 inhibition may be due to full mutated S6K production.

PLC γ 2 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, tropomyosin synthesis (where both cannot promote TXA2 synthesis without PLC γ 2 availability) that both VEGF and tropomyosin are necessary for reactivate G-actin filaments and re purify blood in veins. So why VEGF +tropomyosin is producing white mature cells?? VEGF cannot regulate directly the PLC γ 2 synthesis and consequently can't regulate TXA2 synthesis but TXA2 synthesis cannot be done without PLC γ 2 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 [38].

Old blood cells when passes through spleen will be broken to save iron which bind to PLC γ 2 for regenerate new blood cells by PLC γ 2 which extracted in spleen which are responsible for metals transportations and proliferation for new cells, but inhibition in PLC γ 2 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 PLC γ 2 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 [39].

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 PLC γ 2) by antigen occurs in vivo, leading to down-regulated expression and to an unanticipated modulation of glycosylation of surface IgM. So, inhibition in PLC γ 2 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.

IgM autoantibodies, and the evidence that these 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. PLC γ 2 first regulate BCR activities which regulate both IgM IgD synthesis through synthase regulation, where IgM is more active and less stable than IgD that IgM necessary for modulating and regulating inflammatory immune response and anti-inflammatory processes through modulating T-cells reactivity.

RESULTS AND CONCLUSION

Chronic lymphocytic leukemia [CLL] reflect Inhibition in PLC γ 2 synthesis "may be 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 PLC γ 2 Biosynthesis will reflect reduction or inhibition in thromboxane-A production.

Osteoarthritis "OA" is characterized by a sharp expression in Gamma-Phospholipase C-1 "PLC γ 1" (which catabolize inflammations), with decreasing "or inhibition" in PLC γ 2 "PLC beta" productions (which necessary for immune modulation, for B-cell maturation and for T-cells modulation and regulate TXA2 synthesis). The increasing in PLC γ 1 with Deficiency in Ser amino acids, and deficiency in proper S6K, with decreasing or inhibition in OPA1-synthase activity will lead to inhibition in PLC γ 2 which lead to diabetes and early Osteoarthritis "A" prognosis.

PLC γ 2 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 PLC γ 2 productions 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 decreasing in anti-inflammatory processes of immune productive efficiency.

Also, inhibition in BTK and PLC γ 2 mainly will reflect Inhibition in the two antigens IgM in and IgD synthesis. Chronic lymphocytic leukemia "CLL" reflect decreasing or inhibition on growth-promoting signaling via the B-cell receptor. The Bruton tyrosine kinase (BTK) is the important for PLC γ 2 systems which is necessary for B-cell activities and T-cells modulation. Bruton tyrosine kinase (Btk) necessary to activates PLC γ 2 ,11,12 which necessary to activate thromboxane A2 and necessary for modulating immune activities and T-cells too.

Both Collagen and BTK pathways are necessary tools for re-activating PLC γ 2 which catalyzes arachidonic acid (AA) release to produce thromboxane-A2 (TXA2) synthesis, and necessary for B cells maturation and critical for B-cell receptor (BCR), where, inhibition in BTK and in PLC γ 2 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 PLC γ 2 synthesis and reactivities.

Also, inhibition in the availability of Ser, Tyr, Leu, Pro with inhibition in necessary hydrophobic amino acids synthesis and in BTK and then in PLC γ 2 can lead to Osteosarcoma which is a cancer cases that produces immature bone (due to mutins in PLC γ 2 and in TLR4 productions) found at the end of long bones, often around the knee. Deficiency in proline with inhibition in Ser, Tyr, leu (or

mutations in synthase) and in specific beta-subunits-calcium carrier can reflect mutations in the PLC γ 2 (beta subunits) productions due to deficiency in proper beta-oxidation that can lead to deficiency or inhibition in the PLC γ 2 and PLC alpha , and in MHC class two, that will lead to deficiency or inhibition "or mutations" in "SIRP α 1 and in TLR4, PD-L1 then in PD-L1" lead to isolations to that area (due to precipitation of the un functioned calcium by PLCs) that can lead to mutated immature bone and tissue synthesis.

PURPOSE OF STUDY

Understanding the main reasons for causing chronic lymphocytic leukemia "CLL" where, proper S6K /BTK and PLC γ 2 are main regulations for thromboxane-A synthesis and necessary for B-cells maturation 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 amino acids and mutated S6K production lead to deficiency or inhibition in Ser phosphorylation signaling which normally is the basis of Ser /Thr phosphorylation signalling which necessarily for Akt, S6K1 synthesis and necessary for RORs and IFNs synthesis and also necessary for proper PLC γ 2 productions, where S6K is main regulator for ATPase and for proper PLC γ 2 synthesis , that I have to note that the shortage ratio of amino acids (or enzymes or steps) is the ratio that can define the degree and type of specific disease that can differ from others which can linked together with the same Syndromes of disease , and 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, 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 abscess 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 inflammations molecules and their growth was rapid enough faster than IFNs productions and faster than PLC γ 2 productions due to to the age of the child, "Note some her regular treating doctors diagnosed her medical conditions as a type of Autoimmune disease and she has weakened immunity due to sudden fast infection related to her young age".

HIGHLIGHTS

a) increasing in PLC γ 1 with Deficiency in Ser, in proper S6K, and decreasing in synthase activity with inhibition in PLC γ 2 will reflect decreasing in anti-inflammatory processes, reflect starting or increasing in Osteoarthritis syndromes, and also reflects the appearance of diabetes syndrome.

b) proper healthy PLC γ 2 are so necessary for increasing re-modulate immune efficiencies, and for re-modulate antigen and T-cells refunctions, and also proper healthy PLC γ 2 production are so imp for recovery from osteoporosis and from both Osteoarthritis and diabetes.

c) inhibition in PLC γ 2 Biosynthesis can reflect decreasing or inhibition in Thromboxane-A 1 percentages and its Molecular structure, where CLL characterized by inhibition in BTK, inhibition

in PLC γ 2 synthesis, inhibition in main antigen synthesis, and inhibition in the proper normal Thromboxane-A synthesis which regulated mainly by PLC γ 1 then IFNs production then regulated by PLC γ 2 proper productions.

d) Chronic lymphocytic leukemia (CLL) observed during treatment with B-cell receptor inhibitors pathway including inhibitor of Bruton's tyrosine kinase-PLC γ 2, where CLL can be strongly linked to Osteoporosis "OA" and linked to both Osteoarthritis and diabetes too.

CONFLICT OF INTEREST STATEMENT

The Author declare that the research work has been conducted in the absence of any commercial or financial relationships, that could be construed as a potential conflict of interest.

REFERENCES

- Guoqing Z, Xu C, Zejun L, Honghai Z, Xinpeng Z, et al. (2014) Disruption of phosphoinositide-specific phospholipases γ 1 contributes to extracellular matrix synthesis of human osteoarthritis chondrocytes. *International Journal of Molecular Sciences* 15(8): 13236-13246.
- Xiaolei C, Yue W, Ning Q, Bing Z, Chun X (2020) PLC γ 1 inhibition-driven autophagy of IL-1 β -treated chondrocyte confers cartilage protection against osteoarthritis, involving AMPK, Erk and Akt *Journal of Cellular and Molecular Medicine* 25(3): 1531-1545.
- Ashraf M El T (2021) An in-depth study of TCA cycles, OPA1, S6K1, ATPase, TLR4, MHC-class-1, GCs, and IFNs biosynthesis, and their roles of deficiency in diabetes, asthma, cancer, etc. and the NAD roles in their activities. *Open Access Journal of Biomedical Science* 3(5): 1194-1205.
- Yu, M, Chen, Y, Zeng H, Y Zheng, G Fu, et al. (2017) PLC γ -dependent mTOR signalling controls IL-7-mediated early B cell development. *Nature Communications*.
- Jacob T J, Elisabeth M, Stefen L. N and seth L. M (2021) The role of PLC γ 2 in immunological disorders, cancer, and neurodegeneration. *Journal Of Biological Chemistry* 297(2): 100905.
- Nicola V, Andre S, Cyrus C, Jean-Yves R, Marc H, et al. (2019) Type 2 diabetes mellitus and osteoarthritis. *Seminars in Arthritis and Rheumatism* 49(1): 9-19.
- Khan FA, Paulette BG, Min Z, Leslie SS (2001) Insulin activates ATP-sensitive K^+ channels in pancreatic β -cells through a phosphatidylinositol 3-kinase-dependent pathway. *American Diabetes Association* 50(10): 2192-2198.
- Moran S, Elson A (2019) The roles of protein tyrosine phosphatases in bone-resorbing osteoclasts. *Journal of Biochimica et Biophysica Acta Molecular Cell Research* 1866(1): 114-123
- Katherine RS, Laura JM (2005) Tyrosine phosphatases as regulators of skeletal development and metabolism. *Journal of Cellular Biochemistry* 96(2): 262-77
- Buckbinder L, Crawford DT, Qi H, Ke HZ, Olson LM, et al. (2007) Proline-rich tyrosine kinase 2 regulates osteoprogenitor cells and bone formation and offers an anabolic treatment approach for osteoporosis. *Proceedings of the National Academy of Sciences* 104(25): 10619-10624.
- Timsah Z, Ahmed Z, Lin CC, Melo FA, Stagg LJ, et al. (2014) Competition between Grb2 and PLC γ 1 for FGFR2 regulates basal phospholipase activity and invasion. *Natural Structural and Molecular Biology* 21(2): 180-8.
- Zhu L, Jones C, Zhang G (2018) The role of phospholipase c signaling in macrophage-mediated inflammatory response. *Journal of Immunology Research* 2018(2): 1-9.
- Jean BS, Elisabetta D, Laura V, Nadine VB (2020) The adaptor protein APS modulates BCR signalling in mature B cells. *Cellular Signalling*, Vol. 73.

14. Zhenfeng Y, Seokho K, Roberts F (2017) Phospholipase C γ 1 (PLC γ 1) controls osteoclast numbers via colony-stimulating factor 1 (CSF-1)-dependent diacylglycerol/ β -catenin/cyclinD1 pathway. *Journal of Biological Chemistry* 292(4): 1178-1186.
15. Mun SH, Peter SP, Kyung HP (2020) The M-CSF receptor in osteoclasts and beyond. *Experimental and Molecular Medicine* 52(8): 1239-1254.
16. Gao B, Xu W, Wang Y, Zhong L, Xiong S (2013) Induction of TRIM22 by IFN- γ involves JAK and PC-PLC/PKC, but not MAPKs and PI3K/Akt/mTOR pathways. *Journal of Interferon & Cytokine Research* 33(10): 578-587.
17. Ya-Jen C, Michael JH, Ching CC (2002) Interferon- γ -induced epithelial ICAM-1 expression and monocyte adhesion. *Journal of Biological Chemistry* 277(9): 7118-7126.
18. Lee AM, States DJ (2006) Colony-stimulating factor-1 requires PI3-kinase-mediated metabolism for proliferation and survival in myeloid cells. *Cell Death and Differentiation* 13: 1900-1914.
19. Hui QW, Altomare DA, Kristine LS, Poulikakos PI, Kuhajda FP, et al. (2005) Positive feedback regulation between AKT activation and fatty acid synthase expression in ovarian carcinoma cells. *Oncogene* 24(22): 3574-3582.
20. Zhengfeng Y, Seokho KK, Roberta F, Sahil M, Ali Z (2017) Phospholipase C γ 1 (PLC γ 1) Controls Osteoclast Numbers via Colony-stimulating Factor 1 (CSF-1)-dependent Diacylglycerol/ β -Catenin/CyclinD1 Pathway. *Journal of biological Chemistry* 292(4): 1178-1186.
21. Dailing M, Holly E, Roberta F, Brian U, Deborah VN (2006) PLC γ 2 regulates osteoclastogenesis via its interaction with ITAM proteins and GAB2. *Journal of Clinical Investigation* 116(11): 2869-2879.
22. Shengli X, Jianxin H, Kong PL, Koon GL, Tomohiro K (2009) Phospholipase C γ 2 Is Critical for Dectin-1-mediated Ca²⁺ Flux and Cytokine Production in Dendritic Cells. *Journal of Biological Chemistry* 284(11): 7038-7046.
23. Viviana C, Elisa B, Roberto F, Marina C, Marina K, et al. (2010) Phospholipase C gamma 2 is critical for development of a murine model of inflammatory arthritis by affecting actin dynamics in dendritic. *Plos One* 5(1).
24. Guonping F, Yuhong C, Renren W, James S, Demin W (2012) Phospholipase C γ 2 plays a role in T-cell receptor signal transduction and T-cell selection. *Journal of Immunology* 189(5): 2326-2332.
25. Karen OD, Joseph OF, Cees Van K, Ngaisah KM, Mohamed RD (2017) Properdin and factor H production by human dendritic cells modulates their T-cell stimulatory capacity and is regulated by IFN- γ . *European Journal of Immunology* 47(3): 470-480.
26. Jacob TJ, Elisabeth M, Stephen LN, Seth LM (2021) The role of PLC γ 2 in immunological disorders, cancer, and neurodegeneration. *Journal of Biological Chemistry* 297(2).
27. Smith GF (1980) Fibrinogen-fibrin conversion: The mechanism of fibrin-polymer formation in solution. *Biochemical Journal* 185(1): 1-11.
28. Zhenyu Li, Delaney MK, Kelly AO'B, Xiaoping D (2010) Signaling during platelet adhesion and activation. *Arteriosclerosis Thrombosis and Vascular Biology* 30(12): 2341-2349.
29. Yingqiu L, Tianyi L, Kevin D, Zengyuan L, Yuanyuan L, et al. (2018) Phospholipase C γ 2 signaling cascade contribute to the antiplatelet effect of notoginsenoside Fc. *Frontiers in Pharmacology* 9:1293.
30. Stefan O (2006) Activation of platelet function through G protein-coupled receptors. *Circulation Research* 99(12): 1293-1304.
31. Emily JK, Grigorios K, Sara Z (2021) Regulation of extracellular matrix production in activated fibroblasts: Roles of amino acid metabolism in collagen synthesis. *Frontiers in Oncology* 11: 719922.
32. Lu WJ, Jie JL, Duen SC, Jayakumar T, Tsonng HF, et al. (2011) A novel role of andrographolide, an NF-kappa B inhibitor, on inhibition of platelet activation: The pivotal mechanisms of endothelial nitric oxide synthase/cyclic GMP. *Journal of Molecular Medicine* 89(12): 1261-1273.
33. Wist M, Meier L, Gutman O, Haas J, Endres S, et al. (2020) Ncatalytic bruton's tyrosine kinase activates PLC γ 2 variants mediating ibrutinib resistance in human chronic lymphocytic leukemia cells. *Journal of Biological Chemistry*. 295(17): 5717-5736.
34. Jeong MK, Jinny P, Eun MN, Hyun KS, Sang YK, et al. (2021) Bruton's agammaglobulinemia tyrosine kinase (Btk) regulates TPA-induced breast cancer cell invasion via PLC γ 2/PKC β /NF- κ B/AP-1-dependent matrix metalloproteinase-9 activation. *Oncology Reports* 45(5): 56.
35. Pal Singh S, Dammeyer F, Hendriks RW (2018) Role of Bruton's tyrosine kinase in B cells and malignancies. *Molecular Cancer* 17(1): 57.
36. Fecteau, JF, Bharati, IS, O'Hayre M, Tracy MH, Thomas JK, et al. (2012) Sorafenib-Induced apoptosis of chronic lymphocytic leukemia cells is associated with downregulation of RAF and myeloid cell leukemia sequence (Mcl-1). *Molecular Medicine* 18(1): 19-28.
37. Shivana ML, Adam Utey, Kelvin PL (2019) Survival of long-lived plasma cells (LLPC): Piecing together the puzzle. *Frontiers in Immunology* 10: 965.
38. Francesco PT, Danilo DN, William GW (2021) The role of BTK inhibition in the treatment of chronic lymphocytic leukemia: A Clinical View. *Journal of Experimental Pharmacology* 13: 923-935.
39. Freda KS, Sergey K, Andrew JD, Andrew JS, Graham P (2011) B-cell receptor signaling in chronic lymphocytic leukemia. *Blood* 118(16): 4313-4320.