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Review Article

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Osteoarthritis Linked to Diabetes Characterized Sharp decreasing in Ser /Proline /PLCγ2 with Increasing PLCγ1, Where Inhibiting S6K/BTK / PLCγ2 Affect TXA2 Synthesis Cause C-lymphocytic Leukemia

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ABSTRACT

proper S6K /BTK and PLCγ2 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 PLCγ2 productions , where S6K is main regulator for ATPase and for proper PLCγ1 and for PLCγ2 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 "PLCγ1", with decreasing "or inhibition" in PLCγ2 "PLC beta" productions. The increasing in PLCγ1 with Deficiency in Ser amino acids will lead to deficiency in Ser phosphorylation signalling (which is main basis for Ser/Thr phosphorylation signaling 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 PLCγ2 producions 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 PLCγ1&2, where phospholipase Cγ2 (PLCγ2) 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 PLCγ1&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 proplem. 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 phosphorylations of Ser pathway is so necessary steps and mechanism for normal S6K productions, necessary for IFN-Gamma and for PLCγ1 productions, and therefore necessary for normal PLCγ2 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 Ça+ which 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.

It's imp to note that Tyrosine phosphatase PTPs are important regulator of chondrogenic patterningare 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 osteprogenitor embryonic development, and bone formations.

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Synthetase is the main regulator for PLCγ1 activities followed by synthase effects for beta-subunits ("PLCγ2") productions which is able to "upregulate phospholipase abtivity" for alpha subunits (PLC-alpha) productions for reactivating fibroblast growth factor receptor (FGFR2) and for reactivating antigens and TLR4 productions. Where, PLCγ1 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 , PLCγ1 recruit to CSF-1 is following imp stages for producing PLCγ2 which is necessary for activating anti-inflammatory
where, IFN-γ activates PLC-γ2 via an upstream of tyrosine kinase.

The PLCγ1 and PLCγ2 (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 PLCγ2 producions 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 "PLCγ1" , then beta "PLCγ2", then alpha "PLC-a" subunits respectively) for cartilage synthesis which promote PLCγ2 synthesis necessary for bone growth including antigen and thromboxane-A synthesis.

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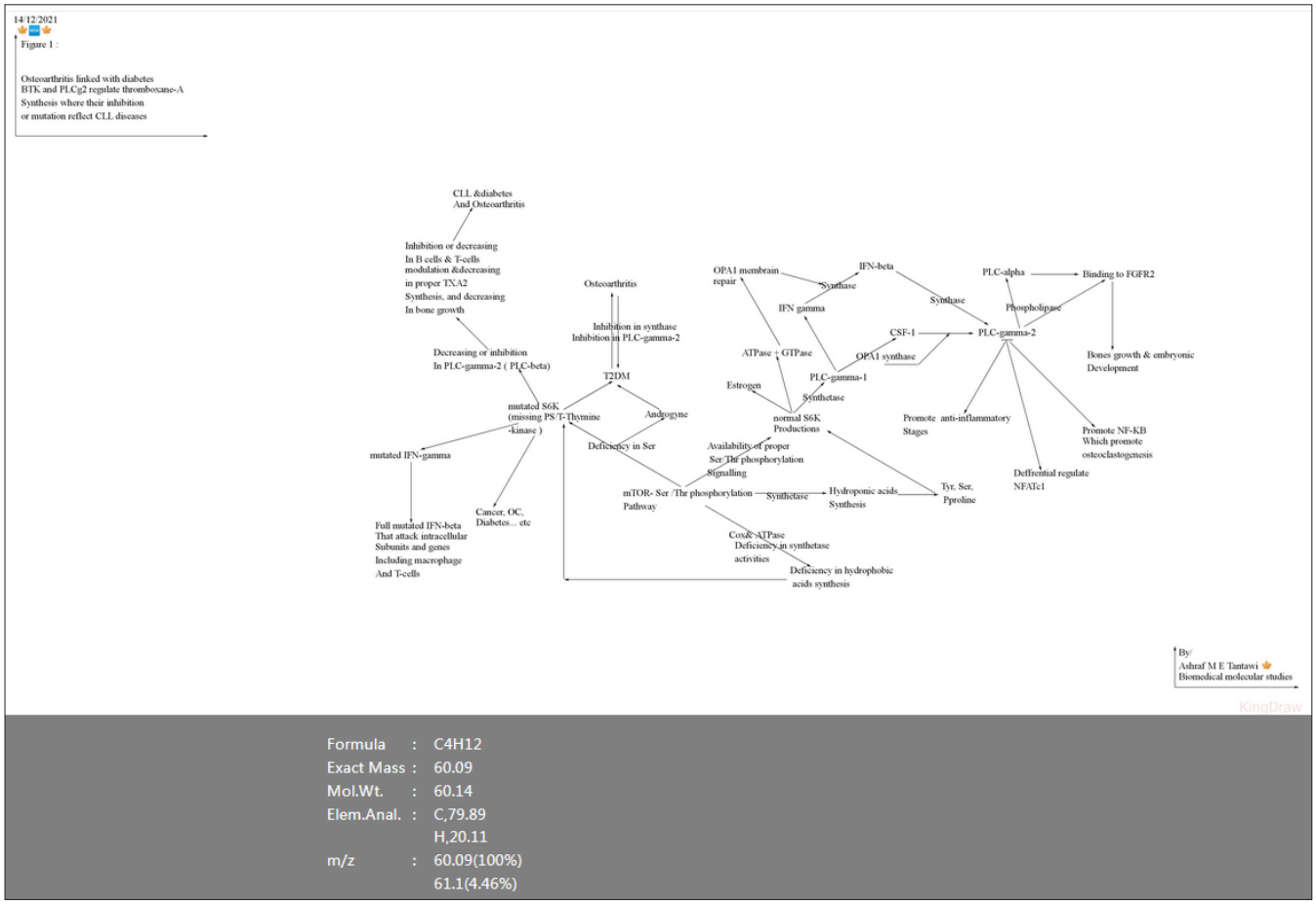

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Mol.Wt.	:	60.14
Elem.Anal.	:	C,79.89
		H,20.11
m/z	:	60.09(100%)
		61.1(4.46%)

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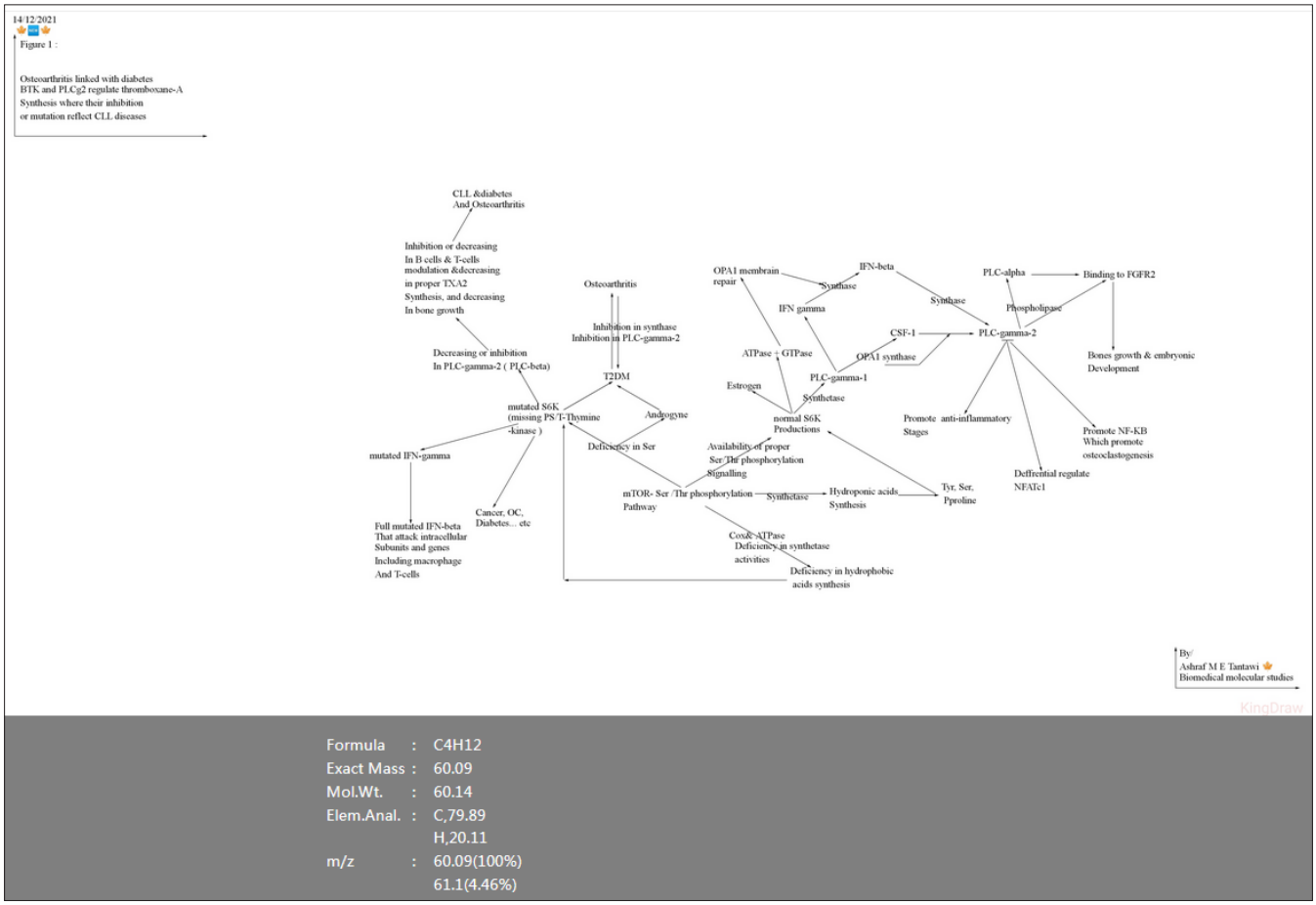

Porpoise of study

Understanding the main reasons for causing chronic lymphocytic leukemia "CLL" where, proper S6K /BTK and PLCγ2 are main regulations for thromboxane-A synthesis and necessary for B-cell maturations and T-cells modulates and functions. 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 PLCγ2 productions , where S6K is main regulator for ATPase and for proper PLCγ2 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 of specific disease from others which can linked together with the same Syndrome of disease, and also the shortage ratio between the beta Cytokines producions and the ratio of 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 regulator disease problems diagnosis.

That, There was a case of a child with 9-year-old who had a suspicion of endosteal bone loss and decreasing in bone growth , and has a sudden infection in the right lung and a lack of breathing with pain . It was found that there was an 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 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 ".

Introduction

Osteoarthritis is characterized by a sharp expression in Gamma-Phospholipase C-1 "PLCγ1", with decreasing in PLCγ2 "PLC beta" which improved by phospholipase oxidations for producing PLC alpha for proliferations and calcum entry ", where PLCγ1 was highly expressed in human OA chondrocytes. which is 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 [1].

That, PLCγ1 basis of inhibition-driven autophagy of IL-1β-treated chondrocyte confers cartilage protection against osteoarthritis. the only presence PLCγ1 has the ability and roles of analyzing biological molecules "Osteoclast" for expressing its own specified functions so, slightly inhibition or decreasing in PLCγ1 will decrease osteoclast and also refunctioning PLCγ1 for reactivating the expression of PLCγ2 which reduce the analyzing function of PLCγ1 and then give the priority to PLC-beta "PLCγ2" 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 [2].

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 PLCγ2 for bone growth and for modulating immune effectiveness.

The Deficiency in the conversion of glutarate to glutamate and decreasing in proline biosynthesis strongly affect on cartilage synthesis due to decreasing in the activation of mitochondrial OPA1 oxidative processes, 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 PLCγ2 then in SIRPα1, and in TLR4 biosynthesis, that can reflect increasing in catabolic analyzing processes that can analyze the phospholipid and interstatium fluid molecules [3].

Method and results

S6K /BTK and PLCγ2 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. 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 androgyne 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 , in OPA1 synthase activities , and in alpha-oxidation with increasing in PLCγ1 will reflect diabetes and increasing in Osteoarthritis"OA" PLCγ1 is a protein molecules that it's activity depending on Tyr phosphatase, and gamma common receptors synthesis which re-activated by JAK STAT signaling which also regulated by synthetase enzyme where synthetase is the main second enzyme in OPA1 chains after COX enzyme (followed by synthase and phospholipase respectively), that proper synthetase enzyme responsible for proper gamma oxidations and for pyrimidine synthesis (or extraction) for hydrophobic amino acids (Ser, Tyr, Leu,...) synthesis, that the proper activity of 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 mediate will creation their receptors then upon synthase enzyme effects will produce active beta-subunits molecules (where, beta subunits chain contain the modified gamma subunits through beta oxidation which contain modified hydroponic a.a., then upon phospholipase effect will promote the alpha-oxidations for more modifications for producing alpha subunits active chain which necessary for 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. That the activities of both PLCγ1&2 are linked to each other and are so necessary for re-activation of B-cells maturation , where, B Cells regulate the productions antigen-specific immunoglobulin necessary for anti-inflammatory processes, 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 and cancers as chronic lymphocytic leukemia (CLL) and can cause several pathogenic problems as diabetes and OA diseases [4].

B-cells are promoted by the function of both PLCγ1& 2, That PLCγ1 synthesis mainly depends on mTOR Ser /Thr phosphorylations signalling pathways (mTS/TP) which produce whether proper active S6K genes or not proper forms which depending on the availability of Ser amino acids in nutrients molecules for running its own necessity phosphorylation pathway "that deficiency in Ser amino acids will reflect decreasing in Estrogen and then increasing in Androgen synthesis which lead to pathogenic diabetes proplem" [5].

Proper S6K synthesis is so necessary for reactivating ribosomal ATPase which is necessary for mitochondrial OPA1 membrain repair (through regulating GTPase productions) where normal OPA1 is necessary for activates and regulating proper PLCγ1 production and its roots of activities pathways which supposed to be completed by creating and producing its second isoforms beta structure form "PLCγ2" upon synthase effect for B-cell maturation, and then for anti-inflammation followed by creating PLC-alpha upon phospholipase functions for promoting proliferation and bone growth through SIRPa and TLR4 productions.

In case of deficincy 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 then the PLCγ2 will not produced or in some cases mutated PLCγ2 can be formed missing necessary hydroponic (Tyr, leu, Pro,... etc) that lwill lead to diabetes, OA, and cancer pathogenesis.

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 in. 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 PLCγ1 productions, "in proper active forms" and therefore necessary for normal PLCγ2 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 Ça+ 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".

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 Cγ2 (PLCγ2) is activated from a variety of cell surface receptors such as SyK "S6K",and BTK which phosphorylate and activate PLCγ2,. S6K1 is the basis for ATPase, and GTPase where, GTPase is necessary for G-prorein 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 productiobs for synthase repair and activity, As, S6K1 is the main regulator for PLCγ1 synthesis and then for PLCγ2 synthesis upon synthase function which later will migrate for beta-cells servival upon production firstly CXCL12 then CXCR4 productions [6].

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 [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 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 PLCγ2 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. And, the low abolition of [Ca2+] i oscillations in the case of T2DM indicates decreasing or inhibition 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 [8].

(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 feedback and by firstly reactivating synthetase (epidermal GF receptor [EGFR], platelet-derived GF receptor) for increasing hyperpolarization and functioning Ca for running necessary bone growth and cellular biosynthesis processes.
The main PLCγ1 proper activities is regulated firstly by proper S6K production from mTOR Ser /Thr phosphorylation pathways and regulated by JAK STAT signaling through productions of Tyr phosphatase, gamma common receptors, and other necessary helical proteins receptors which adopt and activate PLCγ1 and their primary proper productions and functions upon the effects of OPA1 synthetase.

PLCγ1 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 PLCγ1 and then PLCγ2 productions and "which regulated by BTK" for PLC alpha productions for cells proliferation and bones growth. Hydrophobic acids such as Tyrosine, Ser , proline facilitate the survival and proliferation of bones development (and also tumor cells in case of synthase dysfunction and mutated S6K) through facilitating OPA1 oxidative functions (specially proline amino acids) and activate BTK pathways ,Which necessary for FGFR2 gene expression for bones developments.

That, Tyrosine amino acids increase alertness and bone development through activating tyrosine kinases , where, Tyrosine phosphatases are potential therapeutic targets for fighting bone disorders. 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. And, proline-rich tyrosine kinases regulate osteprogenitor cells and bone formations, so Tyrosine and proline (where their synthesis regulated by synthetase) are regulated by PIPs and are critical regulators of multiple stages in bone development [9-11].

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 for creating hydrophobic amino acids synthesis for improving Gamma-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 will activate PD-1, antigens ,SIRPα1, and TLR4 for cells and bone formations and developments .

PLCγ1 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 PLCγ1 competes for a binding site at the very 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 [12]. That, synthetase is the main regulator for PLCγ1 activities followed by synthase effects for beta-subunits (PLCγ2") productions which

is able to "upregulate phospholipase abtivity" for alpha subunits (PLC-alpha) productions for reactivating fibroblast growth factor receptor (FGFR2) and for reactivating antigens and TLR4 productions.

Only Synthetase enzymes are having the ability of hydrolysis molecules, inflammations and phospholipid membranes, but active gamma subunits 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 the beta subunits will protect cells while gamma subunits , and alpha chains containing gamma, beta, and alpha. So PLCγ1 is containing the active gamma chain that can be modified by synthase oxidations for producing PLCγ2 (which contain beta in its molecular subunits) can protect cells through its roles in anti-inflammatory processes and can promote PLC-alpha for proliferation through activating SIRP-a and TLR4.

Some PLCs isoforms are involved in multiple stages in TLR4 and interferon regulatory factors (IRFs) synthesis, indicating that the proper balances of PLCγ1 productions are related to Beta-subunit and alpha subunit balances production" for regulating TLR4 activities (but not vice versa), that PLCγ1 has basic active gamma-subunits that necessary for re-activating or regulating active beta subunits and TLR4 isoforms functions (upon synthase and phospholipase effects respectively), where PLCγ1 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 PLCγ1 productions", that PLCγ1 are containing so necessary regulatory basic amino acids for promoting antigen synthesis, for SIRPα1,, for TLR4 biosynthesis, and then for PD-L1 biosynthesis [13].

Therefore, PLCγ1 can considered as a constructed gamma subunits modified by specific tissue cells for PLCγ1 productions followed by PLCγ2 production that activated by tyrosine phosphatase receptors and by "pTyr" phospho-tyrosine receptors for activating PLCγ2 productions and for PLC-alpha reproduction for bone growth, for B cells maturation, and for promoting anti-inflammatory steps eg mediating PD-1 synthesis and other Beta-subunits, then TLR4, and PD-L1 productions, and basically depend on JAK signaling for SH2B adaptor protein "that is Tyr kinase receptor family" which necessary for BCR mediate B cells maturation", for "pTyr" phospho-tyrosine "Which necessary for PLCs synthesis ", and for SHP1Src homology region 2 domain-containing phosphatase 1 synthesis where are so imp for registrating PLCs synthesis, for B-cells maturation, for bone growth, and for anti-inflammations. Notice that PLCγ2 activated by BTK where PLCγ2 necessary for BCR mediate B-cell maturation which regulated by SH2B adaptor protein so BTK is so necessary for PLCγ2 which necessary for B-cell maturation and also for modulating T-cells [14].

PLCγ1 is accociated with numerous inflammatory diseases in the possibility of reduction or inhibition in PLCγ2 synthesis and in cases of huge infections molecules compared to the limit of PLCγ2 production , that there are considerated limit % between the amount of inflammations from its inflammatory Source activities and the percentage of the productions of gamma and beta phosphorylated active subunits for functioning inflammations then running alpha oxidations for proliferation , but in reduction of beta subunits synthesis compared to amount of inflammations, the gamma subunits will appear to be huge in extra expression associated with information.

PLCγ1 recruit to Colony-stimulating factor-1 "CSF-1" is following imp stages for producing PLCγ2 which is necessary for activating anti-inflammatory where, IFN-γ activates PLC-γ2 via an upstream of tyrosine kinase. The PLCγ1 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 PLCγ1 is recruited to the CSF-1 receptor following exposure to the cytokine. meaning of PLCγ1 recruit to CSF-1 is PLCγ1 following imp stages for producing PLCγ2 which is necessary for activating anti-inflammatory steps then follow the proliferation steps through activating SIRPα1 and TLR4 and then PD-L1 oroductions [15].

So, CSF-1 is a members of the IL-1 receptor family which involved in completing anti-inflammatory cycles for proliferations is regulated by PLCγ1, which regulated firstly by synthetase which necessary for creating necessary hydroponic acids for creating active gamma-subunits productions which define the character of PLCγ1 production for recrcuit to CSFR for PLCγ2 productions and for reactivating antigen for anti-inflammatory stages.

That CSF1R-expressing cells may play an anti-inflammatory role or a cancer-suppressive role. As PLCγ1 recruiting to CSF-1 for PLCγ2 synthesis and PLCγ2 play imp role in anti-inflammations and modulating BCR and T-cells so CSF-1 is playing necessary role in anti-inflammatory processes. And 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 [16,17].

Fibroblast growth factor receptor 2 "FGFR2" (CD332) is a receptors activayed by JAK signaling are so important (throughout synthase and phospholipase regulations) for cell growth (proliferation), cell maturations (differentiation), bone developments (embryonic development). Also, IFN-γ activates PLC-γ2 via an upstream tyrosine kinase to induce activation of PKC-α. so IFN gamma which regulated by synthetase is basically activate the IFN beta Upton synthase effects then activate IFN alpha upon alpha oxidations, but in specific tissue IFN gamma will activate PLCγ2 in the respond to bone growth and anti-inflammation modulations. IFN gamma has the roles of reactivating PLCγ2 , PD1 and MHC class 1 for reactivating MHC class 11 for reactivating macrophage and modulating Tcells. So, PLCγ1 recruited to CSF-1 for proper modulating anti-inflammations and cell-surface protein structure through activating PLCγ2 , and involved in the production of TRIM22 by IFN gamma for mediating antiviral activities and anti-inflammatory processes through modulating IFNs. Due to inflammations ,the increasing in PLCγ1 with decreasing in PLCγ2 "beta" will lead to increasing in gamma oxidation that will increase the analysis of inflammations molecules and main cellular subjects molecules that can reflect osteoclast, but the proper balance of activities between both PLCγ1 and PLCγ2 will lead to osteoblast [18].

Also, the Colony-stimulating factor-1 requires PI3-kinase-mediated metabolism for proliferation So, as PLCγ1 recruited to Colony-stimulating Factor 1 "CSF-1" which involved in anti-inflammations and in proliferation as PLCγ1 has own roles of activities in both anti-inflammations "upon circuit to recruited CSF-1", and in proliferation including bone growth "upon PLCγ2 synthesis" that OPA1 synthase has imp role in PLCγ2 productions [19]. The inhibition of Fatty acid synthase (FAS) activity by

cerulenin or C75 resulted in downregulation of phospho-AKT. Through feedback OPA1 synthase is necessary for reactivating Colony-stimulating factor-1 for reactivating p13k Akt for running proliferation and running anti-inflammations processes. PLCγ2 synthesis activate osteoblast but PLCγ1 production with inhibition in PLCγ2 will activate osteoclast (OC) by inhibiting re-modulating inositol 1,4,5-trisphosphate- PLCγ1&2 are modulating a variety of cellular pathways including osteoclast (OC) differentiation. Where, PLCγ2 production is important for running osteoblast and inhibiting osteoclast, where the increasing in PLCγ1 productions with inhibition in PLCγ2 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" [20,21].

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 PLCγ1 production followed by PLCγ2 productions.

Both PLCγ1 and sphosphoinositide synthase (PIS) are imp for promoting PLCγ2 productions and necessary for proliferations and bone growth, Where, increasing in PLCγ1 "with reduction or inhibitions in PLCγ2 productions will activate osteoclast but the reactivating proper percentage of PLCγ2 synthesis will activate osteoblast. Where, 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), that JAK signaling are playing imp roles in running either osteoclast or osteoblast through mitochondrial OPA1 regulaion activities, that high gamma receptors with decreasing in beta receptors will activate osteoclast but proper percentages of gamma and beta productions (proper % between PLCγ1 & PLCγ2 productions) will activate proper osteoblast through activating PLCγ2 production Which needed for TXA2 synthesis and for beta-cells maturation and activities [22].

PLCγ2 can modulate immune activities and T-cells too , where Bruton tyrosine kinase (Btk) activates PLCγ2 ,11,12 which activate thromboxane A2 re-synthesis

Phospholipase Cγ2 is Critical for Dectin-1-mediated Ca2+ Flux and Cytokine Production in Dendritic Cells [23]. PLCγ2 has a critical activity in dendritic cells, where is having a Critical function for Development of a Murine Model of Inflammatory Arthritis. 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 the capacity of Tcells of dendritic cells [24]. Where,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. It has been reported that Properdin and factor H production by human dendritic cells modulates their T-cell stimulatory. but I report that modulations of T-cells run by the functions of PLCγ2 for re-activating NF-κB by regulating NFATc1, while Properdin subunits composition can modulate NFATc1 or not [25,26].

The increasing in PLCγ1 productions with deficiency or mutation in PLCγ2 will reflect decreasing in B cells maturation and function 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. [Thrombine activation is highly reactivate intermediate the true fibrin monomer and it rapidly, and irreversibly [27,28].

PLCγ2 involved with fibrin formation, where Bruton tyrosine kinase (Btk) activates PLCγ2 ,11,12 leading to thromboxane A2 (TXA2) synthesis. So, PLCγ2 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 PLCγ2 and subsequent DAG-PKC-TXA2 and IP3-[Ca2+] [29,30].

The activation of PLCβ through Gq, which results in the formation of IP3 and diacyl glycerol, plays an important role in mediating αIIbβ3 activation. So, in brief BTK necessary for PLCγ2 producions which is necessary for B-cell maturation and functions, and also PLCγ2 is so imp for thromboxane-A synthesis [31].

Chronic lymphocytic leukemia [CLL] reflect Inhibition in BTK and then in PLCγ2 synthesis which can reflect Inhibition or impaire in Thromboxane-A

Proline amino acids are required for Collagen synthesis where, Collagen binds to its receptors and then activates 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 Bruton's tyrosine kinase "BTK" activates PLCγ 2 variants mediating ibrutinib resistance in human CLL. [32-34].

BTK inhibitors [ibrutinib , CNX-774] significantly attenuated TPA-induced cell invasion and migration in MCF-7 cells and inhibited the activation of the phospholipase Cγ2/PKCβ 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 [35,36].

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 in BTK and PLCγ2 will affect on TXA2 synthesis and will cause Chronic lymphocytic leukemia), and both BTK and PLCγ2 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 PLCγ2 will reflect the Chronic lymphocytic leukemia "CLL" .

Results and Conclusion

Chronic lymphocytic leukemia [CLL] reflect Inhibition in PLCγ2 synthesis "may 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 reduction or inhibition in thromboxane-A production.

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.

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 PLCγ2 systems which is necessary for B-cell activities and T-cells modulation. Bruton tyrosine kinase (Btk) necessary to activates PLCγ2 ,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 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 with inhibition in necessary hydrophobic amino acids synthesis and in BTK and then in PLCγ2 can 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, often around the knee. Deficiency in proline with inhibition in Ser, Tyr, leu (or mutations in synthase) and in specific beta-subunits-calcium carriar can reflect mutations in the PLCγ2 (beta subunits) productions due to deficiency in proper beta-oxidation that can lead to deficiency or inhibition in the PLCγ2 and PLC alpha, and in MHC class two, that will lead to deficiency or inhibition "or mutations" in "SIRPα1 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.

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.

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