Research Article

Mitochondrial Activities Regulate G-Actin Filaments, Regulate TXA2 Subunits and VEGF-A Subunits Synthesis, through Expressing its Anti-Inflammatory Enzymes, which are Playing Imp Roles in Regulating Muscle Contractions, Increasing Anti-Inflammatory Cycles, and the Strengthen of Heart-Beats

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Received Date: November 19, 2020

Publication Date: December 01, 2020

Abstract

Mitochondria are dynamic organelles that contain inner and outer membranes amino acids genes, that move, fuse, and divide according to the needs of the cell through stimulation from ribosomal genes activities for responding and activities of biological molecules in cells tissue metabolism.Mitochondria have a characteristic double membrane structure and function between inner and outer membranes in slightly and widely activities. The inner membrane is fully controlled by ribosome RNAs but the outer membrane is synthesized and controlled by the inner membrane long-OPA1 gene (L-OPA1 gene).

Where the outer membrane is mainly synthesized and controlled by the mitochondrial inner membrane(MIM) to implement the functions of the inner membrane (MIM) and running its programmed processes. The outer membrane is formed through the fusion of s-OPA1 (which divided through the effects of GTPase started from ribosomal functions) and MFN2 gene (which synthesized from inner OPA1 gene membrane), whereas the inner membrane mainly contains the main long OPA1 gene that is regulated by rRNAs activities through specific stimulating processes (from ATPase loops in G-actin and ribosomes) that will be cleaved to L-OPA1 and s-LOP1 games by the effects of GTPase which synthesized from ribosomal functions.

The Proteins involved in mitochondrial outer membrane fusions is 2nd step for outer membrane synthesis (after the 1st steps fission step) is: mitofusin 2 (MFN2, dynamin-related GTPase OPA1 (which encoded by the same gene which encodes the inner membrane L- OPA1 gene) through the regulation of ribosomal ATPase functions, and F-box and leucine-rich repeat_4. The involvement of r-ATPase, F-box, and leucine-rich repeat nucleotides in the synthesis of outer mitochondrial membrane is indicating the values and the necessities of r-ATPase and leucine amino acids and its mitochondrial synthetase enzyme regulations in mitochondrial functions for regulating imp activities in tissue cells metabolic cycles, which responsible for re-synthesis the pyrimidine nucleotides from purines nucleotides in vivo, and indicates the values of the presence of its pyrimidine nucleotides in mitochondrial inner and outer membrane genes, and for its repairs.

Due to presence and availabilities of inflammations in blood vessels and in interstitium fluid will stimulate actin filaments to generate its polarized active isoforms which will transmitted through filaments to cells then to inner cells components for stimulating ribosomes and mitochondria activities for expressing its mitochondrial anti-inflammatory enzymes which are : synthase, phospholipase, and Cox2, and synthetase enzymes, which I consider them as anti-inflammatory regulating enzymes where can act on inflammations molecules and toxic granules for later producing TXA2 subunits then through feedback in vivo will synthesis the VEGF-A subunits for completing the effects on inflammations molecules, and then for re-stimulating G-actin filaments again for endothelin-1 re-synthesis and for reactivate PPARs genes proliferations activities through reactivating MAPK pathways which considered to be very necessary for resynthesis cytokines through the regulation of the synthesised TXA2 "alpha" subunits and VEGF-A "alpha" subunits .

Once the effects of mitochondrial enzymes (ME) on inflammations molecules is done will lead to TXA2 subunits productions which through its feedback will generate VEGF-A subunits where both TXA2 and VEGF-A subunits considered as strong anti-inflammatory alpha subunits tools for regulating the anti-inflammatory beta cytokines synthesis for completing the effects on inflammations molecules in some other cells tissue and in their interstitium fluid where are considered as a protection from many health problems.

VEGF-A subunits are considered to be one of the main strong anti-inflammatory tools, which can be synthesized from both directions: 1st/ from G-actin filaments active polarized isoforms and endothelin-1 synthesis pathways, and 2nd/ from the acting of mitochondrial enzymes on inflammation molecules for TXA2 production than through its feedback will produce VEGF-A subunits, and it is considered as the production of active VEGF-A alpha subunits are the basis of the contractions and relaxations of muscles, veins, and arteries, and also considered to be main for the TNF-a subunits re-expression for blood platelets re-synthesis, for Autophagy functions, for PPARs genes activities, and blood functions.

Endothelial cells (ECs) activities represent the major cell type that interacts for developing anti-inflammatory subunits: TXA2, VEGF, and TNF-a subunits tools, and for developing organs including the pancreas tissue cells and their activities started throughout stimulation between G-actin filaments and ATPase loops (ribosomal and G-actin ATPase loops) for regenerations polarized active isoforms and transmitting them to inner cells and interstitium fluid between cells for re-stimulating ribosomes activities and mitochondrial functions.

The activations to mitochondria occur from ribosomes, from G-actin, and from lysosomes security granules (which stored in some active cells as autophagy) directly or indirectly, where can be started by stimulating the G-actin filaments isoforms activities to produce active polarized isoforms signals "PIS" to be sent across G-actin filaments as polarized signals isoforms "PSI" to endothelial tissue cells "ECs" and to organ tissue islets for producing pro-endothelin-1 and for VEGF-A subunits synthesis. Endothelin-1 active genes and VEGF-A alpha subunits are considered to be strong ani-information tools for purifying blood and interstitium fluid and veins from inflammation toxicity and viral toxicities and also considered to be necessary for the muscle contractions through the regulation of MAPK pathways functions.

Where the re-feedback activities which started by TXA2 alpha subunits for back ET-1 resynthesis are considered as the programmed communication cycles (PCOC) for sending and receiving genes or isoforms messages between cells and to endothelial tissues for adjusting anti-inflammatory cycles, and for PPARs genes functions reactivation, and for ET-1 resynthesis which is so necessary for purifying blood vessels too, and including the removal of inflammations molecules from tissues interstitium fluid.

The presence of inflammation will stimulate mitochondrial activities to produce Cox2 and synthase, phospholipase, and synthetase enzymes which will act on inflammations to produce TXA2 active subunits which are strong regulators through feedbacks for VEGF-A synthesis. Where the increase in TXA2 production is the result of the up-regulation of the VEGF-A subunits in tissues or in the infected tissue and results of filaments and muscle contractions for accelerating the migrations of the synthesized alpha anti-inflammation subunits between cells and tissues.
Increasing in mitochondrial optimal activities, in endothelin-1, and in TXA2, VEGF-A alpha subunits productions reflect the increasing anti-inflammatory processes and are reflecting the optimal contractions of muscles and arteries due to the mitochondrial synthetase, synthase, and phospholipase enzymes productions.

Purpose of this work

Mitochondrial repair and its re-activation by ribosomes are the basis for increasing heart efficiency and re-increase anti-inflammations efficiencies.

Repeat active pentapeptides protein contains the repeated enkephalin Leu-pentapeptides amino acids sequences "Tyr, Gly Gly, Phe, Leu" is optimal active protein for repair mitochondrial inner membrane through reactivation the ribosome functions and regulations.

Mitochondrial synthetase enzyme is the main root for pyrimidine nucleotides synthesis and consequently is the main for muscle contractile mechanisms.

Materials

_polarized G-actin signals isoforms "PIS",

_endothelial tissue cells "ECs",

_ribosomal ATPase,

_Endothelin_1

_(TXA2) Thromboxane-A2, _vascular endothelial growth factor VEGF-A, VEGF_B subunits,

_tumor necrosis

factor-alpha TNF-α subunits,

_Mitochondrial anti-inflammatory enzymes (Cyclooxygenase

phospholipase, and synthase enzymes),

_Mitogen-activated protein kinase (MAPK),

_Repeated pentapeptides PROTEIN contain Leu pentapeptides sequences (RPP)

_ Peroxisome proliferator-activated receptors (PPARs)

Introduction

Inflammation molecules expression first will stimulate both G-actin filaments and mitochondria for producing its effective enzymes for acting on inflammations toxicity which later will produce TXA2 subunits which through feedback will stimulate the VEGF-A subunits synthesis, then will re-stimulate ET-1 reproductions.

Once the effects of mitochondrial enzymes (ME) on inflammations molecules are done will lead to TXA2 subunits productions which through its feedback will generate VEGF-A subunits where both TXA2 and VEGF-A subunits are considered as strong anti-inflammatory tools subunits for protection from many health problems.

VEGF-A subunits are considered to be one of the main strong anti-inflammatory tools in the immune system, which can be synthesized from both directions 1st.: from G-actin and endothelin-1 activities and 2nd: from the acting of mitochondrial enzymes on inflammation molecules for TXA2 subunits productions then through its feedback will produce VEGF-A subunits, and is considered to be the basis of the contractions and relaxations mechanism of filaments, muscles, veins, arteries and fibers and also considered to be main for the TNF-α subunits re-synthesis and blood platelets synthesis.

One of the imp activities of VEGF-A is their strong links to MPAK pathways and Peroxisome proliferator-activated receptors (PPARs), as once VEGF-A synthesized as will activate MAPK pathways and Peroxisome proliferator-activated receptors activities.

VEGF-A subunits are considered to be strong anti-inflammation and anti-viral alpha subunits, that can stimulate endothelin-1 synthesis to purify vessels and interstitium fluid from any impurities including inflammation toxicities, and platelets aggregation.

VEGF-A subunits peptide chain is active chain subunits that are directly acting on foreign molecules and inflammation molecules for producing prostacyclin **(**9**)**.

Vascular endothelial growth VEGF factor-induced prostacyclin productions are mediated by a protein kinase **(**8**)**. Where, VEGF produced from epithelial and other cells tissues that have been stimulated to be synthesized through mitochondrial effects on inflammations molecules to produce first TXA2 alpha subunits then later will produce prostacyclin which is a prostaglandin member of lipid molecules that can inhibit platelet aggregation and activation due to its contents from TXA2 and VEGF-A alpha subunits (indicated its molecular composition includes VEGF-A active sites and TXA2 subunits active sites), where will need the re-activities of mitochondria to induce phospholipase for analyzing and functioning the prostacyclin and prostaglandins contents to prevent its aggregation and blocking blood vessels.

VEGF-À alpha subunits are produced not only by endothelial cells but also by and from multiple other cell types, including heart cells, macrophages **(**13**)**.

VEGF-A alpha subunits can be synthesized from TXA2 subunits and from endothelin-1 pathways Where later can be stored in cells as active lysosomal security granules, where autophagy can re-stored active TXA2 and VEGF-A alpha subunits as securely lysosome granules in their active cells forms, where will be expressed at the time of attacking the toxicity **(**22**)(**my previous research work).

The most necessary nucleotides needed for mitochondrial inner membrane repairs and activities is Leu amino acids **(**3**)**, or in other meaning, the most necessary nucleotides for mitochondrial genes repairs are the pyrimidines nucleotides, where are regulated by synthetase enzyme productions, which originally reactivated by ribosomes functions and then will be stimulated by ribosomes to be synthesized by mitochondrial activities. Where the synthetase active sites will be generated in the ribosomal genes which will activate the mitochondrial membranes repairs.

Cardiomyocytes (CM), the main cell type present in the heart. Which connected end to end by gap junctions, involved in the concerted contractile mechanism, and are the source and the target of VEGF-A alpha subunits, Where VEGF-A alpha subunits activate CM, and inducing morphogenesis, contractility and wound healing. When stressed, cardiomyocytes undergo hypertrophic growth and apoptotic responses in vivo as well as in cell culture models, Such changes predispose to heart failure in the longer term **(**20**)**. On the other hand, VEGF-A alpha subunits are produced by CM during inflammations mechanical stress, and cytokine stimulations **(**16**)**.

During inflammations stress mechanism, the main inflammatory molecules will stimulate epithelial cells which will stimulate the mitochondrial activities in CM to express its full anti-inflammatory enzymes which will produce TXA2 and Prostacyclin which throughout feedback will produce VEGF-A alpha subunits, where the programmed communication (PCO) for sending and receiving genes or isoforms messages between epithelial cells and living cells through interstitium fluid will start by G-actin filaments activities, and through productions the TXA2 alpha subunits,Which will re-stimulate G-actin filaments to produce its polarized isoforms again to be migrated to stimulate inner cells components started by ribosomes which by itself will stimulate mitochondrial activities for producing its anti-inflammatory enzymes which will start acting on inflammatory molecules for producing TXA2 alpha subunits which through its feedback cycles will stimulate VEGF-A subunits synthesis in CM which can be stored as ready active security lysosomal granules, where autophagy can store in its active forms.

But, the decrease in G-actin activities will lead to decreasing in mitochondrial functions and will lead to inhibitions in mitochondrial enzymes expressions, thus will lead to inhibition in TXA2 expression and VEGF-A subunits expressions, that will lead to decreasing in Angiogenesis due to decreasing in PPARs genes proliferations activities, which is strongly connected with TXA2 and VEGF-A alpha subunits activities respectively, then will lead to decreasing in heart contractility activities.

The source of the contraction (including G-actin activities, ribosomal activities mitochondrial activities, then TXA2 alpha subunits synthesis respectively) can be induced increasing in VEGF alpha subunits expression started by G-actin filaments. Prostanoids after synthesis (as I mentioned), can regulate the level of VEGF and bFGF mRNA in skeletal muscle cells with TXA2, PF2a, PE2, and NO restricting VEGF expression, and adenosine enhancing VEGF release **(**18**)**.

Where, the contraction of muscles is directly related to the synthesis of TXA2 and VEGF-A alpha subunits productions, and phosphorylations processes and related to the stimulations to the mitochondrial activities by previous steps to express its anti-inflammatory enzymes, and related to MAPK pathways related to ribosomes ATPase activities.

Where ribosomal ATPase activities will stimulate mitochondria to express and release its anti-inflammatory enzymes (which are so necessary enzymes for regulating contractile processes through the TXA2 and VEGF-A subunits synthesis for facilitating their migration across filaments, arteries, heart, and muscles to re-stimulate actin filaments and endothelial cells again for re-synthesis TXA2 and VEGF-A alpha subunits, and for reactivating the PPARs and MAPK activities pathways for proliferation and anti-inflammation cycles and for resynthesis endothelin-1 genes for continuing the cleaning of veins and interstitium fluid from toxicities.

The contractions processes are regulated and controlled by the availabilities of pyrimidine nucleotides and they're synthesized which regulated by the availabilities of synthetase mitochondrial enzyme (EME), where the pyrimidine nucleotides synthesis are regulated by mitochondrial synthetase enzyme, which regulates the conversion of purines nucleotides to pyrimidine nucleotides in vivo, and that enzyme is directly linked to ribosomal ATPase activities and to the L-OPA1 mitochondrial repair genes, which is activated by ribosome for inner and outer membrane synthesis.

The RNA that has Sense character in human has this structure is: GGGCCTCCGAAACCATGAAC

Where, the Human VEGF which has antisense structure is: GGGCACACAGGATGGCTTGA **(**18**)**, where can indicate that as some purine nucleotides replaced by some pyrimidine nucleotides as will convert the character of the gene from antisense to sense characters and vice versa, and indicated that the synthetase mitochondrial enzyme play valuable regulator roles in the muscles contractions and anti-inflammation functions, where can re-activate the GTPases processes for mitochondrial repairs and then for expression its anti-inflammatory enzymes again for lysis and functioning the prostanoids to prevent their agrégation in the interstitium and blood vessels.

The deficiency in synthetase enzyme will cause a deficiency in pyrimidine nucleotides synthesis lead to accumulation of glucose derivative molecules and accumulation of fatty acids in arteries and veins lead to diabetic diseases and arteriosclerosis and can lead to failure in heart muscle activity.

Endothelial cells (ECs) from the inner cell lining of filaments and blood vessels and represent the major cell type that is linked with developing organs. ECs receive signals isoforms from G-actin filaments and later will stimulate the releasing of alpha subunits to determine cell-fate specification, morphogenesis, and functions of the pancreas **(**2**)**.

As inflammation molecules will exist as will stimulate G-actin filaments and as G-actins will release its available polarized isoforms to be delivered across filaments to cells and inner cells components, and as polarized signals isoforms "PIS" will stimulate cells antigen to translate the received polarized signals to inner ribosomes for producing the active RNAs which carry the necessary active sites for repairing and activating the inner "active" mitochondrial membrane enzyme and its outer membrane synthesis through the fusion mechanism to s-OPA1 genes and MFN2 gene for outer membrane synthesis.

Endothelial tissue cells "ECs", are the basic cells responsible for pro-endothelin-1 synthesis through stimulation and modification occurred to G-actin isoforms by inflammation molecules for stimulations and producing pro-endothelin-1 and VEGF-A subunits.

VEGF-A alpha subunits reflect specific active sites in 1st DNA strand and reflect the activities of G-actin, ribosomes, and mitochondrial activities, where VEGF-A is produced and activated through regulation processes mainly translate the main active sites in 1st DNA strand which represent the activation of the ribosome, mitochondrial function, TXA2 synthase, and consequently represent the VEGF-A synthesis. Where the Deletion in T Lymphocytes will Accelerates Tumorigenesis **(**14**)**, due to the disappearance of alpha subunits from T-lymphocytes which mainly responsible for regulating the beta subunits productions for acting on inflammations and Tumorigenesis as toxic molecules.

Methods

As The inflammation molecules will exist as will stimulate G-actin filaments, and as G-actins will release its polarized active isoforms to be delivered across filaments to cells and inner cells components, and as polarized signals isoforms "PIS" will stimulate cells antigen to translate the

received polarized signals to inner ribosomes as the ribosome will produce its active RNAs which carry the necessary active sites for repairing and re-activating the inner "active" mitochondrial membrane enzyme and its outer membrane synthesis through the fusion mechanism to s-OPA1 genes and MFN2 gene for outer membrane synthesis.

As the mitochondrial inner and outer genes activated as mitochondria will express its anti-inflammatory enzymes on inflammations and toxicity molecules including aggregated molecules, where will produce TXA2 alpha subunits then through feedback will produce VEGF-A alpha subunits.

Endothelial tissue cells "ECs", are the basic cells responsible for pro-endothelin-1 synthesis through stimulation and modification occurred to G-actin isoforms by inflammation molecules for stimulations and producing pro-endothelin-1 and VEGF-A subunits.

As plasma glucose, HbA1c, triglyceride, and free branched fatty acids increase as will start to two ways of stimulations for VEGF-A subunits productions :

1st): is the stimulation to mitochondrial phospholipase, Cox2 and TXA2 synthase production, that will act on & digest accumulated lipid and saturated fatty acids that will lead to TXA2 subunits productions, which through its feedback will lead to VEGF-A subunits synthesis , that will help to act on plasma glucose, branched fatty acids and inflammatory molecules for sharing results in metabolic cycles where will purify interstitium & blood from extra lipid accumulation, and from any inflammations, 2nd): stimulations directly from G_actin filaments through stimulations from inflammations molecules for stimulating the G-actin filaments for expression the active isoforms where through activities of their ATPase loops will lead to activate the polarized active isoforms for stimulating inner cells ribosomes for activating mitochondrial functions for expression its anti-inflammatory enzymes for acting directly on foreign molecules and toxicities for TXA2 subunits productions , then through feedback will produce VEGF-A alpha subunits, where will re-stimulate G-actin for resynthesis endothelin-1 gene for purifying interstitium fluid and blood vessels.

Bone marrow transplantation induces islet expansion through only the synthesis of alpha subunits which regulate the expansion of beta-cell mass and regulations depend on the stimulus for islets **(**4**)**.

Microvasculature plays an integral role in islet functions. The main Factors modulating VEGF-A expressions are the ribosomal functions and G_actin filaments activities (which are expressed due to stimulation from inflammations and toxicities including aggregated molecules), where the ribosomal functions will activate the mitochondrial functions which are all influencing the islet vascularity.

The vascular endothelial growth factors (VEGF) alpha subunits VEGF-A signaling synthesis are necessary for proper islet vessel developments and functions, that are related to mitochondrial activities and the TXA2 alpha subunits productions, and strongly connected to PPARs activities, where VEGF-A alpha subunits synthesis can be synthesized from the feedback from TXA2 alpha subunits and can be synthesized from the endothelial cell's activities through the synthesis of endothelin-1.

As some purine nucleotides in vivo replaced by some pyrimidine nucleotides as will convert the character of the gene from anti-sense to sense characters and vise versa, and indicated that the synthetase mitochondrial enzyme plays valuable regulator roles in the muscle contractions and anti-inflammation functions, where can re-activate the GTPases processes for mitochondrial repairs and then for expression its anti-inflammatory enzymes again for lysis and functioning the prostanoids to prevent their agrégation in the interstitium and blood vessels.

The deficiency in synthetase enzyme will cause a deficiency in pyrimidine nucleotides synthesis lead to accumulation of glucose derivative molecules and accumulation of fatty acids in arteries and veins lead to diabetic diseases and arteriosclerosis and can lead to failure in heart muscle activity.

The improvement of insulin sensitivities directly will be through the reactivating mitochondrial synthetase enzyme which will directly adjust and regulate the pyrimidine nucleotides re-synthesis from purines nucleotides which can be found in plasma and blood as glucose or as branched fatty acids…etc, that due to the regulation by synthetase enzyme will lead to decreasing in plasma glucose, triglycerides, and the extra fatty acids in tissue, and will prevent lipid accumulation, and then will improves insulin sensitivity, and the glucose tolerance, as well as will, reduces pancreatic islet triglyceride content.

The roles of VEGF-A and islet vasculature are controlling the synthesis of alpha subunits, which regulating beta-cell mass depends on the stimulus for the islets **(**6**)**.

VEGF subunits don't regulate blood sugar (but can act on aggregated molecules) and don't increase insulin sensitivity but, the VEGF-A subunit's biosynthesis reflects the mitochondrial activities and its regulations directly depend on synthetase enzyme for the pyrimidine synthesis from purines nucleotides in vivo.

Pre-proendothelin-1 consists of 212 amino acids "where their types and arrangements depending on the primary stimulated polarized active isoforms orders from G-actin filaments activities. Pre-proendothelin-1 is cleaved by dibasic pair-specific endoproteases to form proendothelin-1, a 38 amino acid precursor peptide in humans (Inoue et al., 1989b).

The generation of endothelin-1 from pro-endothelin-1 occurs to release the active Leu - amino acids fragment for resynthesis of the VEGF-A alpha subunits and for the synthesis of sestrin-Leu carrier gene in the liver, that will increase fatty acids metabolism and decrease the aggregation of glucose and branched fatty acids in interstitium fluid in tissues, where ET-1 must contain Tyr, Gly(2), Phe,& Leu that can be reactivated by repeated pentapeptide proteins "RPP" where will have several pathways functions including activating mitochondria, Sestrin in the liver, and reactivating brain enkephalin Leu pentapeptides.

pre-pro-ET-1 (which I consider as it is the polarized modified active polarized signals isoforms received "from G-actin filaments and then modified by epithelial cells ") is an intermediate precursor, which later will be cleaved by the endothelial converting enzyme (ECE) to form the active ET-1, which composed of 21-amino acid peptide and also can be composed of 38 or 40 amino acids depending on the primary active G-actin isoforms molecular structure and depending on the presence of pyrimidine nucleotides in amino acids specifically: Ser, Tyr, Gly(GGT), Gly(GGC), Phe, and Leu amino acids where are so necessary for mitochondrial inner membrane "L-OPA1" gene repairs, and consequently for Enkephalin leu pentapeptides reactivities in the brain.

ECE is directly dependent on mitochondria functions for pro-proendothellin synthesis. Viral infection or inflammations toxicity will stimulate interstitium fluid genes, will stimulate G-actin filaments activities and then mostly all will stimulate mitochondria for expression its anti-inflammatory enzymes (synthase, phospholipase, Cox2, and synthetase) enzymes for acting on inflammations where will lead to TXA2 subunits productions, which through feedback will reactivate VEGF-A productions.

VEGF-A subunits.Cardiomyocytes (CM), the main cell type present in the heart. Which connected end to end by gap junctions, involved in the concerted contractile mechanism, and are the source

and target of VEGF-A, Where VEGF-A activates CM, inducing morphogenesis, contractility and wound healing.

I would like to note that the main for morphogenesis and contractility are the ribosomal functions with its ATPase loops functions and the activities of the mitochondrial enzymes on toxicity and on aggregated sugar and fatty acids including G-protein, where the results will be TXA2 alpha subunits productions that through its feedback process will produce VEGF-A subunits, where all previous steps are the main for contractile processes, but the noted that VEGF-A alpha subunits productions are the contractile factor in muscles, heart, and veins.

Diabetes problems and the contractile mechanism in CM is strongly related and regulated by ribosomal ATPase loops in the ribosome, regulated by ATPase loops in G-actin filaments, and mainly related to the expression of synthetase enzyme from mitochondria for adjusting the pyrimidine nucleotides synthesis from purine nucleotides in vivo, then related to MAPK pathways and the PPARs genes proliferations activities.

Where, due to its optimal activities of mitochondrial synthetase enzyme expression will digest and convert the accumulations of branched fatty acids and glucose in interstitium tissue fluid to pyrimidine nucleotides for adjusting the regulations balance in genes activities in cells metabolic cycles and glands activities, and will prevent the accumulated fatty acids and sugar purine nucleotides in molecules in plasma interstitium fluid.

The optimal function and activities of mitochondrial activities regulated by ribosomal ATPase will increase anti-inflammations efficiency including autophagy synthesis and activities and will increase the synthesis of the stored lysosomal security granules in cells and in autophagy (which represent the TXA2 and VEGF-A alpha subunits) and are stored in autophagy to be in the active forms for acting on inflammations molecules **(**22**)**.

Prostacyclin is derived by modification and activities from some endothelial cells tissue due to the effects of mitochondrial enzymes, then due to the TXA2 subunits productions and functions, then due to its feedback processes for VEGF-A subunits productions and its activities, and due to the function of stored lysosomal security granules in autophagy and some other cells.

Those synthesized Prostacyclin molecules will need the re-activations of mitochondrial anti-inflammatory enzymes to digest the Prostacyclin contents and to free the VEGF-A and TXA2 alpha subunits for further anti-inflammatory cycles.

Mitochondrial enzymes activities, and VEGF-A and TXA2 alpha subunits activities are the anti-aggregatory and vasodilator mediator upon specific activation for ET_1 and farther VEGF-A subunits synthesis for acting on interstitium toxicities and on inflammations molecules to produce again TXA2 and VEGF-A subunits for regenerate endothelin-1 through reactivating the PPARs genes activities and MAPK pathways.

During endothelium-dependent, prostanoid-mediated contractions/constriction, the prostacyclin appears to be a major endothelium-derived contracting factor (EDCF) and is related to the availabilities of phospholipase and synthetase Mitochondrial enzymes activities which is depending on the MAPK pathways activities, and related to the presence of ribosomal ATPase activities.

endothelium-derived contracting factor (EDCF related mainly to G-actin filaments activities due to its ATPase loops activities for phosphorylation activities, and to phospholipase, synthase, and synthetase enzymes productions that when G_actin will be stimulated will produce polarized signals isoforms peptides as a genes signals to be transmitted into endothelial tissue for stimulating two steps 1st will stimulate ribosome activities 2nd will stimulate the productions of modified pre-pro-endothelin for endothelin-1 genes through the effect of ECE, and for VEGF subunits productions.

Cyclooxygenase-dependent responses are exacerbated by aging, obesity, diabetes, or hypertension, and endothelin-1 can potentiate cardiovascular risk factors contractions by promoting prostacyclin production **(**12**)**.

It is not clear to only promote prostacyclin productions for biomedical studies but to declare the promoting to accelerate mitochondrial inner gene L-OPA1 repair for expression the anti-inflammatory enzymes including synthetase enzyme will be clear for TXA2 alpha subunits productions and through feedback for VEGF-A alpha subunits productions where all will act on inflammations molecules for prostacyclin productions which will need again the mitochondrial activities for digesting its content for preventing sugar and fatty acids aggregation in plasma and blood vessels.

Thromboxane A2 TXA2 alpha subunits are the endogenous ligand for the prostanoid TP receptors where derived from prostaglandin in vivo due to the effects of mitochondrial enzymes and VEGF-A subunits on prostaglandin molecules where through feedback will restimulate the TXA2 alpha subunits re-synthesis and re-synthesis the VEGF-A subunits again upon the anti-inflammatory cycles.

TXA2 is a strong stimulator for increasing the PPARs proliferation genes activities upon the activities of phospholipase+TxA2, Synthase, and synthetase enzymes, that can reactivate the MAPK pathways for VEGF-A subunits productions through its feedback processes then will restimulate G-actin filaments again for ET-1 re-synthesis for cleaning interstitium fluid and blood vessels from toxicities and inflammation months.

TXB2 productions and activities are regulated and controlled mainly by the synthesis of TXA2 alpha subunits through acting on inflammations molecules by the effects of mitochondrial TxA2 Synthase and phospholipase enzymes.

The Omega-class cytosolic glutathione transferases (GSTs) have distinct structural and functional for mitochondrial repairs and stimulating ribosomal activities. Mammalian GSTO1-1-catalyzed glutathionylation or deglutathionylation of a key signaling protein may explain the requirement for catalytically active GSTO1-1 in LPS-stimulated pro-inflammatory **(**23**)**.

Glutathione S-transferases (GSTs) are regulated by ribosomes functions and by its ATPase loops activities and is a necessary enzyme for mitochondrial activities and for its repair where transferase enzyme analyze the transfer of amines, methyl or methyl groups for re-synthesis L-OPA1 mitochondrial inner membrane gene during its repair but in a limit, where transferase can transfer +ve cation for reconstructing genes too, that will not desirable in some problems of diseases, where can inhibit ribosomal activities and genes activities.

Fluorine linked with anti-thrombin biological molecules is playing imp role to facilitate anti-inflammation genes, increasing blood fluidity, and accelerate endothelin-1 and VEGF-A subunits synthesis where can facilitate the cleaning of veins and plasma from toxicities by endothelin-1. Where, Pentoxifylline can perform the improvement of blood flow in bone and muscles, which can facilitate the blood flow for mitochondrial and ribosomes activities, for G-actin activities and its isoforms transmission access filaments, and for running anti-inflammation cycles.

Results and Conclusion

Diabetes problems and contractile mechanism in CM is strongly related and regulated by ribosomal ATPase with its phosphorylations activities and regulated also by Mitochondrial synthetase enzymes functions and activities which is the basis of pyrimidine synthetase from purines nucleotides that when is in its optimal activities will convert the accumulation of

branched amino acids and glucose in interstitium tissue fluid to pyrimidine nucleotides for adjusting the balance of cells and glands metabolism and prevent the accumulated fatty acids and sugar molecules in plasma. The optimal function and activities of mitochondria regulated by ribosomal ATPase will increase anti-inflammations efficiency including autophagy availabilities and activities and will increase the stored security lysosomes which represent the TXA2 and VEGF-A alpha subunits which are stored in autophagy ready for acting on inflammations.

Mitochondrial repair by OPA1 genes or related repeated pentapeptides genes contains the necessary active sites for mitochondria optimal repair is so necessary for reactivating mitochondrial functions for expression its enzymes (synthase, phospholipase, synthetase,) for acting on toxicities and inflammation molecules for later will produce TXA2 alpha subunits which through its feedback will stimulate VEGF-A alpha subunits for restimulate G-actin filaments and resynthesis endothelin-1 for cleansing veins and interstitium fluid from toxicities and inflammations too.

Endothelin-1, VEGF-A & TXA2 alpha subunits can act on inflammations as anti-inflammatory tools and can act on microbes as anti-microbial tools that can reactivate the MAPK pathway's activities for reactivating PPARs genes proliferations functions.

The increase in TXA2 subunits productions through increasing mitochondrial activities will lead to an increase in its feedback for reactivating VEGF-A subunits activities, thus will be the results of increasing PPARs proliferation functions lead to an increase in blood functions and immune efficiency.

Thyroid enlargement and glands enlargement can be due to one of the following reasons: 1) is the decrease in synthetase, phospholipase, and in TXA2 synthase enzymes, and thus will decrease TXA2 alpha subunits production, and then inflammation and toxicities will increases,

2)The second reason is the isolation of gland cells through the presence of blockage in their capillaries, so VEGF does not reach cells.

Acute thymic involution "ATI" is occurred due to decreasing in the synthetase and phospholipase enzymes and then in TXA2 production and reduction in its feedback for VEGF-A subunits synthesis.

It is clear to mention that the reduction in synthetase, phospholipase enzymes and TXA2 synthase can & will lead to a reduction in muscles contractile activities and will lead to atherosclerotic cardiovascular disease, but it is not clear to mention that Low-density lipoproteins cause atherosclerotic cardiovascular disease **(**25**)**.

Conflict of Interest Statement

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

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Volume 1 Issue 4 November 2020