Research Article

VEGF-A Subunits Originated from Stimulation to G-actin Filaments to Produce Polarized Signals Isoforms where will be Modified by Endothelial Cells & Tissue Islets to Produce Modified Pro-endothelin-1 then ET-1 & VEGF-A Subunits which are Strong Anti-inflammatory Tools, and is Imp for Muscle Contraction & Relaxation in Presence of Cox2, and can be Reactivate by TXA2 Subunits Productions.

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Purpose of this work:

To re-increase immune efficiency.

Abstract

VEGF-A subunits are considered to be strong anti-inflammatory tools and are the basis of the contractions, and relaxations of muscles, veins, arteries and fibers, and are mainly for the reconstruction of blood platelets again with their proper TNF-a and TGF-ß subunits for re proper blood fluidity and functions.

Endothelial cells (ECs) activities represent the major cell type that interacts with developing organs including the pancreas.stimulations occur from stimulator factor to specific tissue cells through stimulating the G-actin filaments activities to produce active polarized isoforms signals "PIS" to be sent across G-actin filaments as polarized signals isoforms "PSI" to be transmitted to endothelial tissue cells "ECs", then those "PSI" which have specific active biophysical structures will be modified by endothelial cells and organ tissue islets to produce pro-endothelin-1 and VEGF subunits VEGF-A & VEGF-B, where VEGF-A considered as strong ani information and strong tool for purifying blood and interstitium fluid from inflammation toxicity and viral toxicity.
Those transmitted polarized signals isoforms vary in their peptides arrangement and specificities depending on the type of stimulator factor and depending on the ATPase degree of activities.

Pre-proendothelin-1 consists of 212 amino acids "where their types and arrangements depending on the primary stimulated orders from G-actin filaments and depending on receiver tissue specificities" containing a characteristic hydrophobic secretory sequence at the amino-terminal. Pre-proendothelin-1 is cleaved at Lys51-Arg52 and Lys91-Arg92 by dibasic pair-specific endoproteases.

VEGF-A can be prepared and used as a recombinant monoclonal antibody, which offers several advantages of activities including:
- High batch-to-batch consistency and reproducibility
- Improved sensitivity and specificity due to its strong relations and connections to G-actin filaments.

The inflammatory cytokines are the result of generating stimulations from the effects of the stimulator of inflammations molecules through the activities of phospholipase enzyme, COX-1& COX-2, TxA2 synthase enzyme on inflammation molecular that will produce TXA2 subunits which can re-feedback to activate VEGF-A subunits for re-functioning the result of enzymes (Cox2, TXA2 synthase, and phospholipase) which acted on toxic inflammation molecules, and thus TXA2 can reactivate G_actin filaments activities through reactivating VEGF-A through re-backpack activities, which is so imp steps of the TXA2 activities for reactivate VEGF-A subunits for purifying blood and removing inflammations molecules from tissues interstitium fluid.

Stimulated G-actin filaments isoforms will generate polarized signals isoforms "PSI" which transmitted to endothelial tissue for promoting the productions of modified proendothelial isoforms signals "MPEIS ", that will generate endothelin_1 and VEGF subunits by the effect of endothelial cleavage enzyme ECE, that the synthesized ET-1 will activate MAPK pathways activities and PPARs to induce necessary proliferation for the needed metabolic cycles...

So inflammatory cytokine is a result of the activation of AMPK proteins under the control of ribosomal ATPase for Cox2 and TXA2 production by Cox2 and TXA2 synthase, and phospholipase enzymes for producing TXA2 active subunits which are the strong regulator for feedbacks for VEGF-A activities. That the increase in TXA2 production is the result of the up-regulation of the VEGF-A subunits in tissues or in the infected tissue for removing inflammation toxic molecules.

Glands enlargement can be due to one of the following reasons:

1) is the lack of COX-2 productions and TXA2 synthase enzymes, and thus TXA2 will not be produced, and thus inflammation increases with not digestions and functioning by VEGF-A,

2)The second reason is the isolation of gland cells through the presence of blockage in their capillaries, so VEGF does not reach the site of inflammation to functioning & recruit its contents,

3)The third reason is there is a lacking & deficiency in the activity of G_actin filaments in the gland, so VEGF-A will not be produced from endothelial cells through modified pro-endothelin-1 productions, thus inflammation will be increased without digestion by VEGF-A subunits.

Endothelin-1, VEGF-A & B, TXA2, and TXB2 can act as antimicrobial & anti inflammations biological tools, with the help of COX-1 activities which reflect the cytochrome and ribosomal ATPase with MAPK pathways activities.

Materials

As polarized signals isoforms "PIS" endothelial tissue cells "ECs",G-actin isoforms, ribosomal ATPase, Cytochrome, VEGF-A and VEGF-B subunits, TXA2 subunits, Cyclooxygenase (COX), phospholipase enzyme, COX-1& COX-2, TxA2 synthase enzyme.

Introduction

Endothelial cells (ECs) from the inner cell lining of blood vessels and represent the major cell type that interacts with developing organs including the pancreas. ECs receive signals from the developing pancreas to grow and, at the same time, release signals to determine cell-fate specification, morphogenesis and function of the pancreas **(**2**)**.

When a specific stimulation occurs to specific cells tissue through G-actin filaments activities "that received their main feeds & control from their cells ribosomal genes with their ATPase activities, and from cytochrome activities for preparing effective peptides for G-actin isoforms activities to be sent across G-actin filaments as polarized signals isoforms "PIS" to endothelial tissue cells "ECs", then those PIS "which have specific biophysical structures, will be modified by endothelial cells and tissue to produce pro-endothelin-1 and VEGF subunits.

Those transmitted polarized signals isoforms by G_actin filaments vary in their peptides arrangement and specificities depending on the type of stimulator factor and depending on the ATPase degree of activities.

When those isoforms signal will arrive at pancreas tissue cells, then ECs will receive those polarized isoforms signals "PIS" from developing pancreas cells for growth and improvement needed metabolic processes, and then will release developed isoforms modified signals(DmIS) to determine lipid cells processes to be developed for resynthesis new modified genes for recycling lipid metabolism, and alpha & beta cells synthesis, for the favor of the 1st primary signals messages received from the 1st stimulated G_actin isoforms genes across filaments and bloodstream.

DmIS can be considered as vascular endothelial growth factors (VEGF) for performing specific improvements needed for specific metabolic cycles where DmIS or VEGF are the modified results from the polarized primary isoforms signals received from G-actin isoforms activities, they have been modified & developed by Pancreatic islets and endothelial cells "ECs" to follow its new

improvements pathways functions including developing alpha subunits for beta subunits synthesis, and for removing impurities and inflammation toxic molecules from tissues interstitium fluid and blood vessels, and also for running lipid metabolic cycles.

vascular endothelial growth factors"VEGF" alpha and B subunits will be increased in patients due to, stress, and due to stimulation which occurred by G_actin filaments isoforms, where their biosynthesis structures are varies depending on their cells specificities in functions, and due to the type of stimulator factor that causes stimulations to G-actin filaments, and due to the interstitium fluid qualities of compositions between cells with pointing at their bio-physical bio-organic compositions structures too.

The vascular endothelial growth factor (VEGF) begin with VEGF-A which regulates and control VEGF-B synthesis and activities and can be re-activated from TXA2 subunits under the effect of phospholipase and, COX-2, and TXA2 synthase enzymes, for regulating the uptake and transcytosis of long-chain fatty acids and their trans-activities over the endothelial tissue such as the pancreas, heart, brain, and skeletal muscle metabolic cycles effect, and for purifying interstitium fluid and vessels from toxic inflammation molecules, and for cooperations for performing many other modified biosynthesis cycles activities.

Methods and Results

In type 2 diabetes mellitus "T2DM" acute insulin response (AIR) is correlated to VEGF-A, but not VEGF-B which correlated to the presence of VEGF-A with specific presentations and arrangements of amino acids, and correlated with plasma glucose, HbA1c, triglyceride, free fatty acid if still found **(7)**. Regular VEGF-A which has a specific main origin root from their stimulated G-actin filaments, which has strong relations to their cytochrome and ribosomal ATPase genes activities and has a strong correlation with plasma glucose appearance & their percentages, HbA1c, triglyceride, free fatty acid, but VEGF-B has the strong origin correlations only to their main VEGF-A modified subunits production, stabilities, and activities.

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

1st) is stimulation to a phospholipid, Cox2 and TXA2 synthase production, that will act on & digest accumulated lipid or saturated fatty acids that will be the result of TXA2 productions,

which will start to reactivate VEGF-A subunits synthesis through feedback, that will begin to act on and re functioning the result of 1st previous reaction of Cox2 and its other partner enzymes on accumulated fatty acids & lipid, that will purify interstitium & blood from extra lipid accumulation, and any inflammations, stimulate the

2nd) stimulations directly to the nearest G_actin filaments through stimulation to cytochrome and ribosomal ATPase for either two pathways

a) Production of TXA2 through Cox2, or

b) Productions of pro-endothelin-1 from tissue islets and from endothelial cells which will be stimulated to release specific stimulated polarized signals isoforms peptides with specific amino acids availabilities and arrangements to be transmitted to reach pancreatic tissue cells for releasing the modified developed isoforms signals "MDIS" for removing inflammation and for continuing & completing the functions as an answer to the primary signals messages received from G_actin filaments. Bone marrow transplantation induces islet expansion, it does not induce the proper expansion of beta-cell mass, where many research data indicate the roles of VEGF-A and islet vasculature on the regulations of beta-cell mass depends on the stimulus for islets **(**3**)**.microvasculature plays an integral role in islet function. Factors modulating VEGF-A expression "which are G_actin isoforms activities" influence islet vascularity and, consequently, influence the amount of insulin delivered into the systemic circulation **(**8**)**. vascular endothelial growth factors (VEGF), Vegfa/Vegfb-Vegfr2 signaling are necessary for proper islet vessel development and functions, that started from endothelial cells activities, but not started and related directly to the initial formation of beta-cells and alpha-cell **(**4**)**.

Systemic breaking "inhibition" of VEGF-B signaling prevents tissue lipid accumulation, improves insulin sensitivity and glucose tolerance, as well as reduces pancreatic islet triglyceride content, under T2DM conditions **(**5**)** .That the digestion "inhibition" of VEGF-B signaling will induce availabilities to the active VEGF-B to bind with accumulated lipid for resynthesis its alpha form VEGF-A under the control of phospholipase and, COX-2, and TXA2 synthase enzymes to produce TXA2 subunits to reactivate VEGF-A for lipid metabolic cycles and resynthesis directly their new VEGF-B again from the available fatty acids in tissue, and re-functioning them and the triglycerides for cells and tissue metabolic cycles, that will prevent lipid accumulation, and then will improve insulin sensitivity and glucose tolerance, as well as reduces pancreatic islet triglyceride content.

The roles of VEGF-A and islet vasculature are in the controlling and regulations of beta-cell mass depends on the stimulus for the islets **(**6**)**, but, in regards to VEGF-A subunits biosynthesis indicates is controller and regulators directly to the islet vascular and VEGF-B productions and activities.

Pre-proendothelin-1 consists of 212 amino acids "where their types and arrangements depending on the primary stimulated orders from G-actin filaments and depending on receiver tissue specificities" containing a characteristic hydrophobic secretory sequence at the amino-terminal. Pre-proendothelin-1 is cleaved at Lys51-Arg52 and at Lys91-Arg92 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 through an unusual enzymatic cleavage, at the Trp (21) -Val (22) sites **(**10**)**, and cleavage can occur at lys, and Arg sites (Inoue et al., 1989b) if fou in pro- endothelin molecular chain to release the active Leu gene fragment for sestrin-Leu carrier activities, that'll contain Tyr, Gly(2), Phe,& Leu that can be responded to reactivate brain activities through endothelin-1 with the availabilities of acetyl CoA and MAPK pathways activities and may need to gain more other amino acids for helping the Phosphorylation as Ser and Thr amino acids, and the containing active Ser amino acids in endothelin_1 are necessary for activating acetylcholine through reverse acetylcholine transferase process to reform choline and acetyl for brain activities in the presence of G-protein.

pre-pro-ET-1 which I consider it as it is the polarized modified signals isoforms received from their stimulated G-actin filaments, that pre-pro ET-1 is an intermediate precursor, which later will be cleaved by the endothelial converting enzyme (ECE) at specific sites to form the active ET-1, which composed of 21-amino acid peptide depending on their tissue specificities and depending on the type of stimulator factor, that also can be composed of 38 amino acids **(**10**)**, or 40, or less depending on the type of stimulator factor and tissues specificities :

H-Cys(1)-Ser-Cys(2)-Ser-Ser-Leu-Met-Asp-Lys-Glu-Cys(2)-Val-Tyr-Phe-Cys(1)-His-Leu-Asp-Ile-Ile-Trp-OH

And it can be also composed of and contain :

H-Cys(2)- Trp-Thr Ser- Val- Tyr--Ser-Cys(2) - Thr -Ser-Ser -Cys(1)-His

-Leu-Met- Asp-Lys-Glu- Thr -Cys(2)-Val-Tyr- Gly(2) -Phe-Leu- lys - Thr- Asp- Gly -Ile- Ile- OH

Depending on ages, and on tissue specificities and the metabolic atmosphere at that time of primary activities.

Notice the pro- endothelin cleavages will be at Val site or at lys with Arg amino acids sites for releasing the imp chain that contains Tyr +Gly+ Gly +Phe+ &Leu to be completed later for the activities of AMPK and TOR protein activities with Cys, ser, Thr a, a, and for sestrin-Leu carrier activities for many metabolic cycles in the brain, in the liver, in heart, in spleen and respiratory tissue, and all will cooperate again together for receiving the stimulated G-actin filaments signals again in vivo.

ECE is membrane-bound, is active at specific polarized active sites, sensitive to metal anions and cations, and to polarized active sites linkages appear through phosphorylations, and also related to the presence of Val, Arg, and lys, amino acids in pro-proendothellin amino acids chain, that cleavage by ECE will be at the site of Val, lys, Arg a.acids.

ECE appears to be a distinct enzyme that has high specificities to modified genes which primarily received from the stimulated G_actin filaments by endothelial tissues, and is strongly related to ribosomal ATPase functions and activities.

VEGF -A can be prepared and used as a recombinant monoclonal antibody, which can be used as a strong anti-inflammatory and anti cytotoxic effective tool, may directly by using VEGF-A for increasing tissue efficiency directly (but we've to know that VEGF-A from males has to be for males, and from females are for females), also TXA2 subunits can be used for reactivate VEGF-A in vivo but also following sex rules is so Imp for successful results. VEGF-A offers several advantages of activities including:

- High batch-to-batch consistency and reproducibility

- Improved sensitivity and specificity due to its strong relations and connections to G-actin filaments.

The activation of p38 results in the up-regulation of COX-2, another inflammatory mediator that can increase VEGF production **(**14**)**.

The inflammatory cytokines are the result of stimulations from the effects of the stimulator of inflammation molecules to G-actin filaments isoforms for generating polarized signals isoforms genes which transmitted to endothelial tissue for promoting productions of modified signals

endothelial pro genes, that will generate endothelin_1 and VEGF subunits that will last as due to the effects of ECE that ET-1 will activate MAPK pathways activities and PPARs to induce necessary proliferation not only in tumor tissue but also in the needed tissues.

Inflammatory cytokine is a result of the reaction of inflammation molecules with a phospholipase, TXA2, and cox2 enz with AMPK & TOR proteins under the control of MAPK pathways roles on inflammation content and cytotoxic molecules that will be the results of the up-regulation of the VEGF-A subunits productions for feeding back reactivating the synthesis of VEGF-A subunits in the infected tissues for cleaning and purifying interstitium fluid and blood vessels.

the putative mechanisms for VEGF induction as well as the existence of positive feedback between VEGF and PI3K/MAPK signaling pathways in T. Gondii-infected retinal pigment epithelium **(**16**)**.

VEGF-A subunits originated in cell tissue at the time of infection or inflammation stimulation effects on inner cell components for releasing needed enzymes as cox2 and TXA2 synthase for TXA2 productions, then by feeding back will reactivate VEGF-A productions.

VEGF-A subunits productions cab be from involved AMPK & TOR protein peptides in the reaction processes of the phospholipase, cox2, and TXA2 enzymes on cytotoxic molecules and inflammations contents, there will be the results of TXA2 productions and feeding back for VEGF-A synthesis and activities for cleaning tissue from impurities and cytotoxicities.

Or VEGF-A subunits can be synthesized in vivo from the stimulations directly from cytotoxic components to the G-actin filaments to release polarized isoforms signals subunits that will form pro-Et-1 which will directly form ET-1 and VEGF-A subunits to purify tissue and to induce its functions effects & activities on inflammatory effects through lysis & functioning the molecular components of inflammation molecules for useful cell metabolism through activating PPARs the proliferation -activities, that will be under the control and the promotion of MAPK active pathways and AMPK with TOR proteins activities which are controlled mainly by actin and ribosomal ATPase activities and cytochrome functions too.

VEGF-A can be purified and exist from its main VEGF-B subunits through a direct translation process that will specify for releasing VEGF-A, and may protease cleavage enz will be needed for cleavage at lysine, valine, or at Arg sites, that will promote translations transcription processes for production the VEGF-A then will activate PPARs active proliferator tools in interstitium fluid

between cells for needed activities for purification under the control of MAPK pathways activities and their protein AMPK &TOR peptides activities.

Notice, the previous mechanism can be understood by researchers as there is positive feedback between VEGF and PI3K/MAPK signaling pathways **(**16**)**.

VEGF at urgent time of infections will be produced directly as I mentioned before, but at safety normal life living VEGF will be modified under MAPK pathways and PPARs active proliferator genes effective tool, that will be stored in cell form as T-cells or macrophages that controlled and protected by its cell ribosomal genes signals activities and cytochrome activities, that surrounding interstitium and blood cells will be protected from effects from macrophages by the presence of TNF-α in their construction and the presence of cytochrome and ribosomal ATPase in ready proper effective functions most of the times,, that if blood will lose the TNF-α, VEGF-A within T-cells or macrophages will start to digest those platelets under the stimulation of COX-2, and TXA2 synthase productions.

Both the lipid prostacyclin and the peptide endothelin-1 "which are modified from primary isoforms genes that received from G_actin signal isoforms genes", are the most powerful endogenous vaso-constrictors, while prostacyclin which is derived by modification from the same endothelial tissue but originated from different stimulated G-actin isoforms, which is a potent antiaggregatory and vasodilator mediator upon specific activation to prostaglandin, that the presence of COX-2 with TXA2 and VEGF-A will increase its abilities for lysis aggregated blood platelets which lack TNF-α for reconstructing new platelets with its normal origin of regular construction of TNF-α, and TGF-β subunits in its origin, that will increase the normal blood functions with neurovascular metabolic processes…

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 COX-2 activities which is fully dependent on the presence of VEGF-A subunits, MAPK pathways activities, and related to the presence of AMPK protein activities.

endothelium-derived contracting factor (EDCF related mainly to G-actin filaments activities, and to COX-2 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 the producing modified pre-pro-endothelin for endothelin-1 genes by the effect of ECE, and for VEGF subunits productions whether through ET-1 synthesis or TXA2 synthesis from the effect of Cox2 and TXA2 synthase enzymes.

Such cyclooxygenase-dependent responses are exacerbated by aging, obesity, diabetes, or hypertension, and endothelin-1 can potentiate cardiovascular risk factors contractions by promoting prostacyclin production **(**11**)**.

Prostacyclin can be reduced by endothelin-A (ETA) receptor antagonists when (ETA) is bonded to cations (Ca+) +ve linkages during smooth muscles contraction and its genes composition structure are fully related to tropomyosin composition structure and activities which considered to be a full regulated by G-actin filaments tools functions and activities.

Thromboxane prostanoid (TP) receptors on vascular smooth muscle cells become hyperresponsive to EDCF under pathophysiological conditions, while IP receptor responsiveness diminishes.

Thromboxane A2 TXA2 is the endogenous ligand for the prostanoid TP receptor where derived from prostaglandin H2 under the influence of thromboxane synthase Tanabe and Ullrich (1995).

Thromboxane A2 (TxA2) is generated by the sequential action of three enzymes – phospholipase A2, COX-1/COX-2 and TxA2 Synthase (TXAS). TxA2 was originally described as being released from platelets, macrophages, neutrophils, and endothelial cells, and serves as a positive-feedback mediator due to & during platelet activation **(**17**)**.

TXA2 is a strong stimulator after produced from the effect of Cox2 and other two other phospholipase+TxA2 Synthase enzymes, that can reactivate VEGF-A subunits productions and activities, "TXA2 has the abilities of the feeding back to VEGF-A till restimulate G-actin filaments again ", may through the reactivation of VEGF-B2 through translations processes, to start its activities as an anti-inflammation tool controlled by VEGF-A for lysis all inflammation molecules and lysis the results from the three enzymes – phospholipase A2, COX-1/COX-2, and TxA2 Synthase (TXAS) activities during removing blood platelets aggregation.

TXA2 contain specific active sites that can activate VEGF alpha and beta subunits for acting as anti-inflammation tools for cleaning interstitium fluid and blood from cytotoxic molecules.

Now, TXB2 productions and activities are due to the received stimulated signals polarized genes from actin filament activities which have been stimulated primarily due to cell ribosomal activities, and are due to the production of TXA2 from acting the TxA2 Synthase and phospholipase on blood platelets for removing their aggregations.

I would like to give imp Notice that, aspirin is a stimulator for Cox2 productions and activities primarily from respiratory cells to stimulate their G-actin filaments activities that their polarized signal genes will be transmitted to respiratory cells, to the liver, to the spleen, and to bone marrow endothelial cells to produce modified Cox2 genes, that previous steps are depending on ATPase and phosphorylations activities, and blood fluidity.

Fluorine elements can play the same roles as aspirin that has a strong role in blood fluidity and is carrying imp roles to facilitate anti-inflammation genes, and blood fluidity, and when bind with endothelin-1 and VEGF-A can accelerate the removing impurities and precipitation from blood vessels and from interstitium fluid between cells "some of the active thrombin inhibitors contain active Fluorine linkages ".

Results

Cyclooxygenase (COX)-2 expression has been found in a variety of human cancers, where Cox2 and TXA2 can be produced originally due to stimulation from both cytochrome with ribosomal ATPase activities to G-actin filaments activities till will stimulate endothelial cells to produce pro-endothelin-1 and VEGF subunits, but TXA2 and COX-2 can be produced separately from different tissues origin with the main specificity for a specific function, and from different G-actin isoforms, genes structures to be joined together for performing their cooperated steps.

The deficiency of specific elements and some imp branched amino acids "eg Tyr, Ser, Gly, Leu" in actin isoforms compositions or endothelin-1 genes or Cox2 or TXA2 genes structures will lead to inhibition in their activities, and may lead to delay or appearance of COX-2 in some cases (eg in some cancers), and delaying in its main function that supposed to be done with endothelin-1, with VEGF subunits, and with TXA2, eg: for proliferation, for removing impurities precipitated molecules from interstitium fluid, and blood vessels.

Endothelin-1, VEGF-A & B, TXA2 and TXB2 can act as antimicrobial & anti inflammations biological tools, with the help of COX-1 activities that reflect the cytochrome and ribosomal ATPase with MAPK pathways activities.

The deficiency in sestrin-Leu carrier activities or deficiency in one or more amino acids in its compositions Ser, lys, val, Thr, Gly or Leu will reduce ribosomal functions and activities and will reduce G-actin filament activities in VEGF-A synthesis and TXA2 subunits productions. Also, deficiency in PPARs genes activities with a deficiency in Cox2 production will reduce TXA2

productions, thus will reduce the effective VEGF-A subunits production, thus will be the result of reducing the anti-inflammation process and cycles in tissues, and maybe the results of increasing of cytotoxic molecules in the blood and tissues, thus may lead to Arteriosclerosis, then heart failure.

Also, deficiency in phospholipase, TXA2synthase, and COX-2 enzymes will reduce TXA2 subunits productions and consequently will reduce VEGF-A subunits synthesis & productions, thus will lead to an increase in toxicity in blood and will reduce anti-inflammatory functions in tissues and the blood vessels. Thus increasing in TXA2 subunits productions will lead to an increase in the feedback for reactivating VEGF-A subunits activities, thus will be the results of increasing blood functions and immune efficiency, thus will be a protection tool from arteriosclerosis, from capillaries blockage, front lipid accumulations, and om toxic molecules from viral infections.

Thyroid enlargement and glands enlargement can be due to one of the following reasons:1) is the lack of COX-2 productions and TXA2 synthase enzymes, and thus TXA2 will not produce, and thus inflammation increases with not digestions and functioning by VEGF-A, 2)The second reason is the isolation of gland cells through the presence of blockage in their capillaries, so VEGF does not reach the site of inflammation to functioning & recruit its contents, 3)The third reason is there is a lacking & deficiency in the activity of G_actin filaments in the gland, so VEGF-A will not be produced from endothelial cells through modified pro-endothelin-1 productions, thus inflammation will increase without digestion by VEGF-A subunits.

Also, deficiency in specific elements (eg fluorine and phosphorus) can be the main reason for glands enlargement, tumors synthesis, and atherosclerosis problem cases.

Acute thymic involution "ATI" is occurred due to decreasing in the enzymes phospholipid and TXA2 synthase that will result in a reduction in TXA2 production and reduction in feedback with VEGF-A subunits, with over stimulations to G-actin filaments lead to overexpression of modified isoforms signals(MIS) "VEGF "received from actin stimulations, lead to overproduction of VEGF A then VEGF-B that will lead to enlargements in a vessel, fibrohyaline changes of the basement membrane of vessels and thymic epithelium.

Also, atherosclerosis can be due to reductions in Cox2, phospholipase and TXA2 subunits productions lead to a reduction in feedback with VEGF-A, lead to a reduction in anti-inflammation efficiency, lead to increase in impurities and toxicities in blood, thus will cause

precipitation of toxicity in blood vessels and fibrohyaline will changes of basement membranes of vessels.

Sepsis is due to a full reduction in TXA2 production and full inhibition in feedback by TXA2 subunits for activating VEGF-A subunits leads to increases in inflammations toxicities in blood and tissues. ascites-derived T cells secrete VEGF and express VEGFR-2 upon activation. Vascular endothelial growth factor directly suppresses T-cell activation via VEGFR-2 **(**18**)**.

VEGF-A belongs to specific active sites in 1st DNA strand which is the main controller for 2nd DNA strand, that VEGF-A is performing its activities only for the favor of their 1st DNA strand functions and surviving, where the VEGF-A Deletion in T Lymphocytes Accelerates Tumorigenesis **(**19**)**.

VEGF-A subunits peptide chain is active chain subunits that are ready to react directly to foreign molecules and inflammation through a metabolic process for completely lysis the foreign molecules and functioning their units in the favor of cell metabolism.

VEGF-A subunits are considered to be strong anti-inflammation and antiviral, that have the abilities to purify vessels and interstitium fluid from any impurities including inflammation and platelets aggregation at urgent hard situations of health problems, but VEGF-A subunits can be presented in specific structures formation of a certain type of cells to be in special protections and have their self-sufficiency and inner metabolic activities as "T-cells" that has self-efficiency, protected in normal steady-state, that in case of problems or danger will be stimulated by TXA2 and Cox2 to start acting on foreign molecules through its free amino acids peptides antigen thread which located covered their cell membrane, where the no of those free amino acids thread varies in numbers between 25 a.a~to 45 ~to 90 free amino acids, that are connecting to their main composition of antigens peptides chain, and may during danger Stat the VEGF-A will order their VEGF-B to lysis their main inner cells components for full appearance in so strong active forms controlled by VEGF-A subunits.

VEGF subunits act not only on endothelial cells but also on multiple other cell types, including macrophages **(**20**)**...

I would like to mention that, you can notice that I usually mention in some of my writings the expression of "metabolic cycles" and I did not use the expression of "processes", because the meaning and the concept of the metabolic cycle of cell is a natural & normal basic concept in normal cases of normal necessary living, that all of the normal important cycles of cells have to

be done together or in steps related to each other to be completed & continued in the basic necessary activities and functions in the favor of 1st DNA strand, heart, and neuron activities cycles in the human body and again I repeat it for continuing the general basic and normal and the activities of the neuron and the activity & for heart activities and all the activity of all body.

But the separated "individual reactions or processes " is the exit of the gene and enzymes or antibodies from its normal metabolic cycle and cycles pathway course to complete outside urgent reactions and separated processes especially for the favor of basic previous normal metabolic cycles, such as elimination of foreign bodies, or lysis blood clotting, or during anger that most of the organs of the body are excited and stimulated by G_actin filaments activities for producing extra VEGF subunits without inflammation, that causing disruption and delaying of some basic metabolic cycles for many organs for producing more VEGF-A subunits that will be the main for platelets digestion in blood vessels, that if will continue & increased will be a health problem will occur in the basic cycles of the body.

MT-ATP8 the mitochondrial gene which encodes ATP synthase membrane subunit is the responsible regulator for TXA2 synthase activities and is responsible for the final step of oxidative phosphorylations in the electrons transport chains.

The reductions in mitochondrial activity will be the result of TXA2 synthase reductions consequently will be the result of anti-inflammation reductions. The most effective sites in that gene are Containing: Tyr, isoleucine, leucine, Gly, Phe, Leu, amino acids respectively, where are so related to enkephalin Leu-pentapeptides functions and full related to Leu activities whether through sestrin activities with Leu, or 2nd DNA strand translations processes.

Mitochondrial activities is so responsible tool for enzymes synthesis specifically Cox2 and TXA2 synthases enzymes which are produced from the mitochondrial membrane through translations process in the favor of inner mitochondrial overlapped genes which represent specific active sites in the main 1st DNA strand which differs in females than males, [that 1st DNA strand in males can be used in females as 2nd DNA strand].

The 46-nucleotide overlap in the reading frames of the human mitochondrial genes MT-ATP8 and MT-ATP6…

The most effective nucleotides in those genes are Tyr, Gly, Phe, and Leu amino acids that can contain more other amino acids as Ser and therein which are necessary for AMPK and their

enzymes cleavage activities, which later will be for modified peptides for several activities as feedback, and some so micro cyclopeptide cycles for protein, lipid, and glucose metabolic cycles.

The reduction in Leu activities or sestrin Leu effective carrier tools activities will be the main results of reductions in chromosomes activities and in mitochondrial regular activities for producing effective enzymes for phospho oxidative respiratory processes and cycles. The changing or missing the Leu and Tyr with Gly will interrupt all neuron microvessel cycles and will interrupt sestrin Leu production and activities also will be the reasons for the reduction in PPARs and TXA2 productions and feedback with VEGF-A subunits, that lead finally to delaying in molecules functioning and precipitation in interstitium lead to tumor and dysfunction in blood pathways activities, and lead to capillaries blockage and arteriosclerosis.

We can say specific diseases has the symptoms of increasing of peptides and glycerol in plasma interstitium fluid and blood, but we didn't give the clear expression of the increasing of their percentage in blood and tissue interstitium fluid and why.

TXA2 synthase enz can produce directly from specific active sites with specific arrangements of active sites in the mitochondrial membrane through direct transcription in specific normal situations of health, but through translations in some other hard of health situation.

After synthase, biological molecules produced from the mitochondria membrane will be moved to actin filaments just beside mitochondria to be polarized & activated in a proper percentage of the active bonding energy in its active sites by ribosomal ATPase and by G_actin filaments ATPase activities, which placed on and attached to the endoplasmic reticulum surrounding nucleus for specific proper short biological cycles including polarization to genes molecules which later will serve for specific higher metabolic cycles.

Rough cytoplasmic reticulum which may serve as actin isoforms peptide containing & reflect specific active sites in chromatin in the nucleus, and can act as a reviewer for gene synthesis from chromatin then be activated by ribosome then transfer to mitochondria for farther activated biophysical and biological structures.

Chromatin is a gene peptide chain constructed from nucleolus by translations or transcriptions to be ready in the forms for other genes synthesis. As those chromatin active sites differ from their original chain as enzymes and other genes will differ in their main constructions, consequently, many processes as enzymes synthesis will be inhibited or will differ in functions. Thus chromatin in tissue cells in females is different from the same tissue cells in males, thus

that will force me to believe drugs for females will be different than males to keep their immune in better conditions.

The gene MT-ATP6 contain the identical amino acids arrangements that necessary for sestrin-Leu active carrier tool and for activations and communications with Enkephalin Leu pentapeptides in the brain which is Tyr, isoleucine, Leu Gly, Phe& Leu, respectively but I expect in steady other situations it supposes to be Tyr, Gly(2), Phe, and Leu as Leu pentapeptides in the brain which is responsible for feeding tissue cells with imp responds for their message through its arrangements amino acids which are including leucine which is the most imp amino acid for metabolic cells cycles and basic for tRNAs productions and dependent on MAPK pathways activities and thus on ATPase and mitochondrial activities".

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