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Pyrimidine TAT TAC Kinases Promote B-Arrestins and Rac1 for Adopting Myocardial Constrictions and Gpcrs Ratio by Ang2-AT2 Synthesis and Anti-Inflammatory Growth

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ABSTRACT

The orphan nuclear pathway (regulated by pyrimidine TAT and TAC kinases and OPA1 enzymes) has the roles of producing the Beta-subunit (fatty Acyl-COA-beta) upon the effects of synthase which regulate B-arrestins synthesis for adopting ACE for Ang2-AT2 synthesis from Ang1-AT1 (that adopt GPCRs ratio) . The inhibition in synthase and in pyrimidines kinases will reflect Inhibition in Acyl-COA-beta synthesis followed by cholesterol and long fatty chains accumulations with high affinity to bind with k and Na salts that can precipitated and cause lipotoxicity. B-arrestins play a well established role in the dampening of G-protein coupled receptors (GPCRs) accumulation, that prevent their increasing through its adopting to ACE for activating Ang2-AT2 synthesis from Ang1-AT1.

The absence of pyrimidine kinases or Ser and Leu with availability of purines kinases produced from Thr phosphorylation can convert the agonist characters of MR to antagonist due to decreasing in adopting MR functions (decreasing in building proper promoters in the active MR molecules). The Glucocorticoid-beta and Estrogen Receptors are so important for producing B-arrestin in Myocardial layer for adopting ACE which placed particularly on ECs for adopting Ang2-AT2 synthesis (adopt Ang1-AT1 ratio to prevent accumulation of GPCRs), and activate the regulated VEGF-A "regulated basically pyrimidine kinases ".

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The mineralocorticoid are necessary for protecting heart from Hyperkalemia and from Hypertrophic cardiomyopathy (HCM) where heart muscle becomes hypertrophied (which due to increasing in GPCRs which will activate the growth throughout increasing in CTGF activity without control by B-arrestins and by Ang2-AT2) with increasing in long fatty chains and cholesterol that can have high affinity to bind to K and Na to cause Hyperkalemia. The decreasing in the pyrimidine kinases "TAT and TAC " kinases will reflect accumulation in Ang1-AT1, in cholesterol and in long fatty chains with decreasing or inhibition in GCs and B-arrestins synthesis that will cause left ventricular hypertrophy (LVH).

As Pyrimidine kinases regulate Estrogen receptor 1 (ESR1), as are necessary for adopting the VEGFA regulations in adipose tissue through B-arrestins synthesis that adopt Ang2-AT2 synthesis which carry the role for adjusting VEGF-A for the regulated proliferation processes. Pyrimidine kinases regulate B-arrestins productions to adopt the Recruit of Gps which simplify in Ang2-AT2 through activating ACE domains which appear in the improvements of both of CMs and endothelial cells functions through creating and adjusting the appropriate pulses in Myocardium heart layer for pumping blood to all tissues cells.

Src kinase (TAT kinases) activation are the trigger in ischemic injury which is parallel to PKC (TAC kinases) which responsible for CpG production for migrating molecules, that both Src kinases TAT and TAC kinases cooperating together for building active promoters responsible to adopt and migrate molecules (such as GC-beta, B-arrestins and Ang2-AT2) for adopt endothelial and CMs cells activities and adopt heart pulses.The tyrosine kinase-mediated mechanisms of ischemic preconditioning, through its role in promoting GC-beta and then B-arrestins (mediated by estrogen availability) for adopting Ang2-AT2 (angiotensin II) synthesis which adjust endothelial functions and immune activities.

Atherosclerosis due to decreasing in pyrimidine kinases synthesis with decreasing in synthase functions, and decreasing in estrogen synthesis which basically depends on Ser phosphorylation pathway that lead to decreasing in Acyl-COA-beta production (decreasing in synthase beta oxydation) that consequently will reflect decreasing in Carnitine palmitoyltransferase-1 (CPT1) synthesis and decreasing in both GCs-beta and B-arrestins productions followed by accumulation of long fatty chains and cholesterol that high affinity of binding with k and Na salts for causing Hyperkalemia. It's important to confer that the TAM receptors kinases functions has the important roles for promoting and activating myocardial functions and protect heart pulses activities through activating Acyl-COA beta production (regulated by hydrophobic domain) which promote GCs-beta upon beta oxidation (regulated by beta oxidation by synthase and by Carnitine Palmitoyl Transferase) followed by B-arrestins synthesis (regulated by GCs-beta and Estrogen) which stimulate ACE functions for Ang2-AT2

synthesis followed by VEGF-A synthesis which activate the anti-inflammatory growth, then followed by the releasing of free AXL receptor from TAM receptors to be migrated to endocardial layer to blood stream. But, inhibition in the TAM two domains Tyro3 and MerTK receptors will lead to inhibition in Myocardial functions that will lead to heart failure with the association of the AXL receptors domain.

Introduction

RORs pathway are necessary for Estrogen synthesis and consequently for Acyl-COA-beta synthesis which promote IFN-beta and GC-beta necessary for B-arrestin (the adaptor protein) productions that adopt ACE activities and Ang2-AT2 productions from Ang1-AT1 which followed by regulating full angiogenesis. The pyrimidine kinases, estrogen, and glucocorticoids synthesis regulated by nuclear orphan pathways (regulated by OPA1 enzymes) which produce fatty Acyl-COA-beta which are the basic for all cardiac endothelial proper developments and functions includes Cardiomyocyte and endothelial cells activities.

The hydrophobic amino acids synthesis that regulated by Proline active amino acids functions and basically by synthetase enzymes functions necessary for pyrimidine synthesis are necessary for tyrosine, Leu, Ser that are necessary roles for regulating proper cellular pathway including increasing the immune effectiveness and heart functions.

In mammalian myocardium, each Cardiomyocyte is surrounded by an intricate network of capillaries and are next to endothelial cells, where the Endothelial Cells adopt and Guide Cardiomyocytes. That the ACE enzyme are located on the surface of ECs for receiving glycoprotein that bind with B-arrestins then activate the Ang2-AT2 synthesis which adopt Cardiomyocytes cells activities and ECs functions then followed by activate VEGF-A synthesis for anti-inflammatory growth.

The B-arrestins activate ACE for converting excess of Ang1-AT1 to Ang2-AT2 within myocardium layer in heart, while the Acyl-COA-beta can be activated in myocardium for reactivating the GCs-beta and mineralocorticoid "MR" which has the roles to bind to Na and K for adjusting the pH and protecting heart muscles from hardening and from Hyperkalemia toxicity then will migrate to skins pores and Kidney to get rid of the K and Na binding molecules.

Materials

_Pyrimidine TAT and TAC kinases _OPA1 membrane
_ROR-beta necessary for Estrogen synthesis and Acyl-COA-beta
_GCs-beta and IFN-beta
_B-arrestins and Ang2-AT2
_Mineralocorticoid "MR"
_Endothelial cells "ECs" and CMs built heart layers
_angiotensin-converting enzyme "ACE"
_Peroxiredoxin
_estrogen
_AXL membrane
_The TAM receptors which are a family of three receptor tyrosine kinases include AXL receptors and hydrophobic domains .
_S6K
_G-protein couple receptors "GPCRs"
_carnitine palmitoyltransferase
_serine palmitoyltransferase
_Polyunsaturated fats
_Rac1

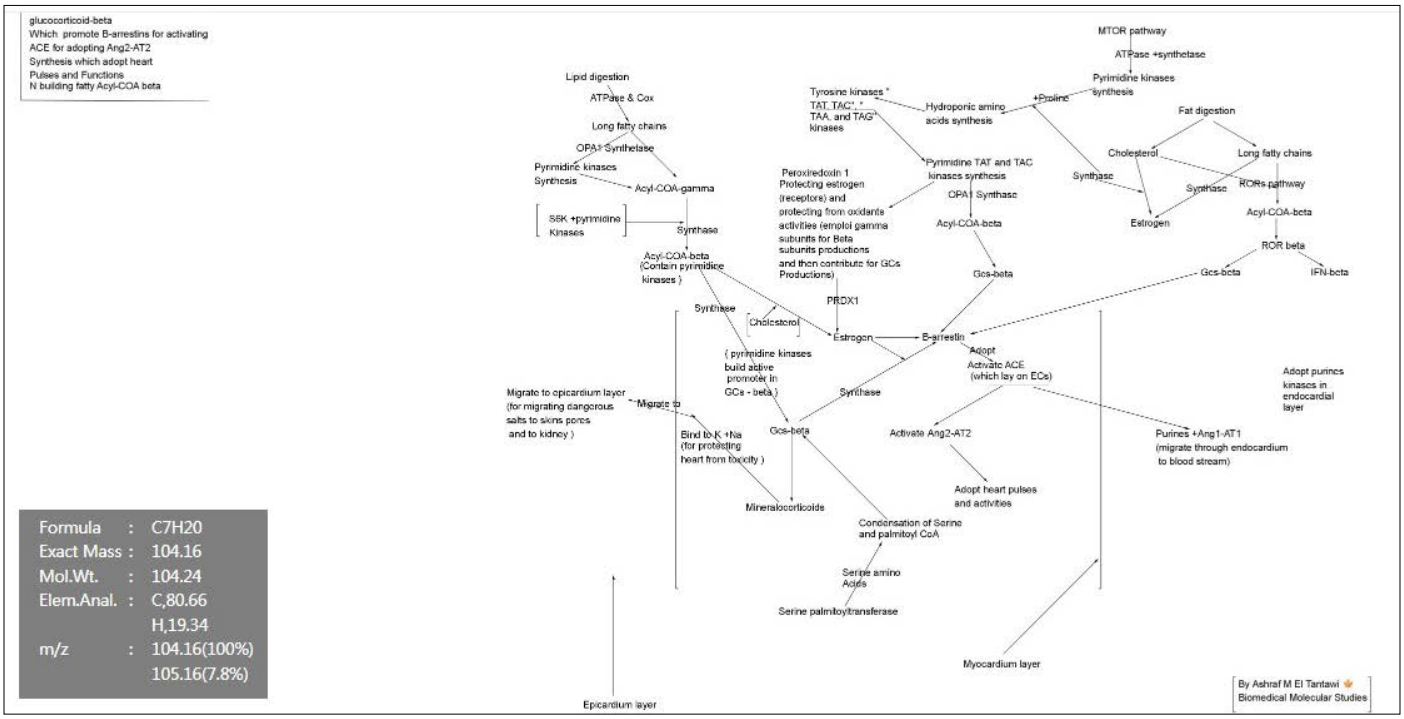
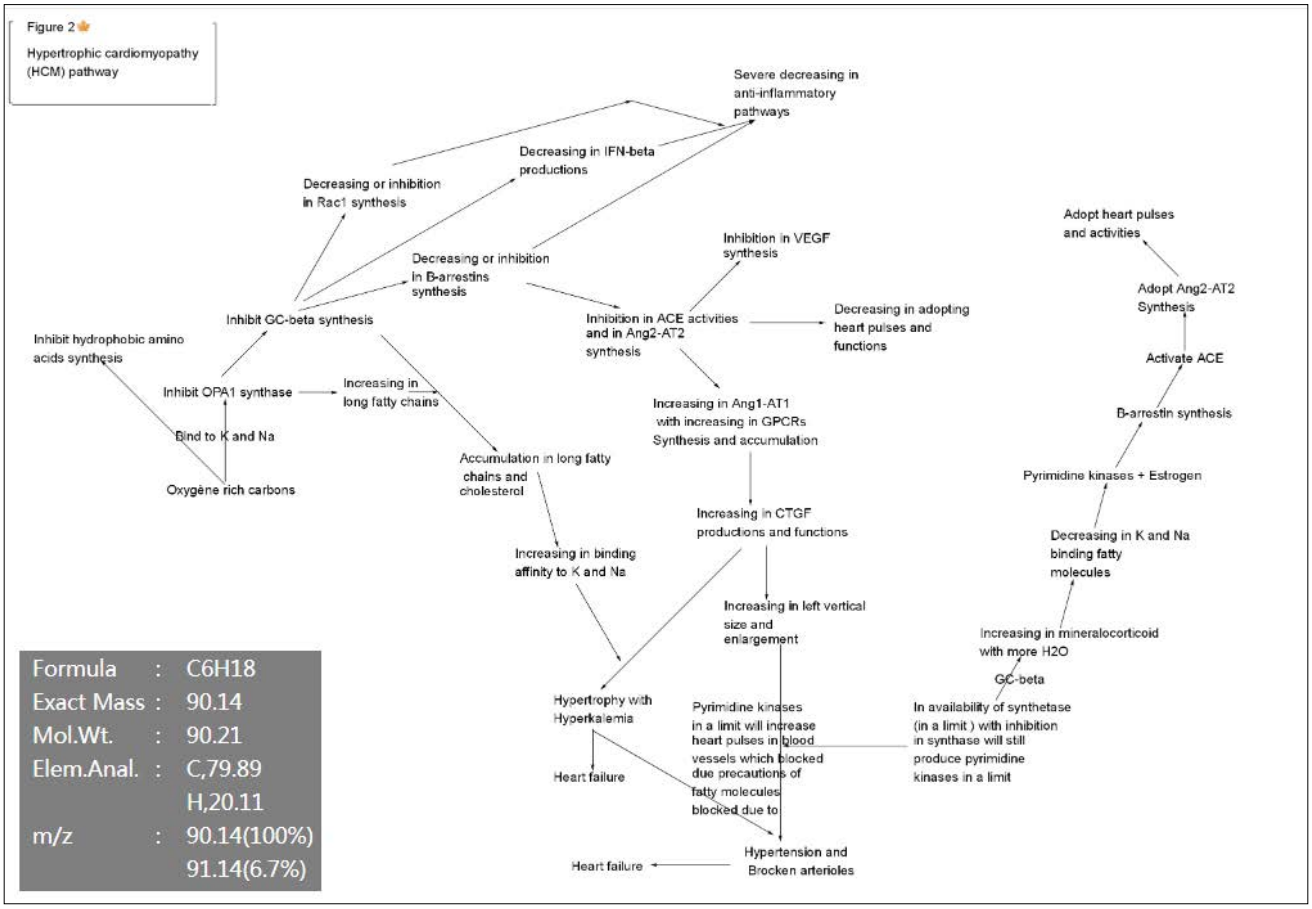


Figure 1



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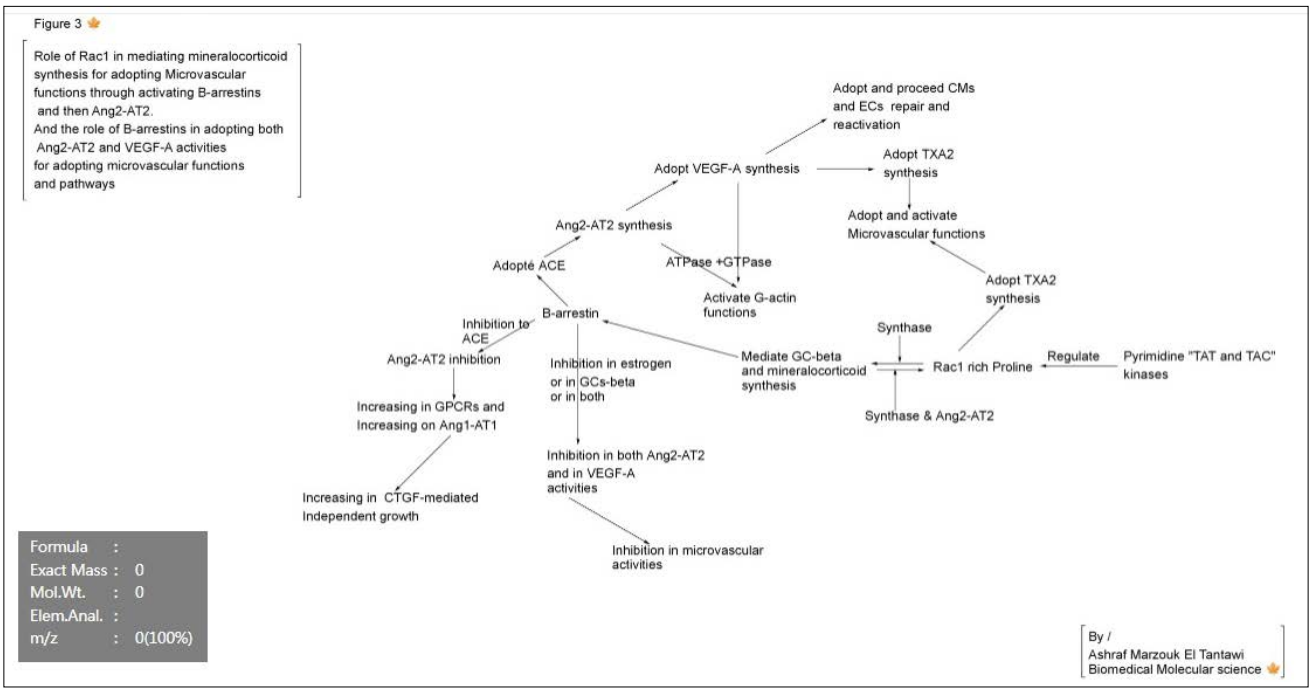

Figure 3

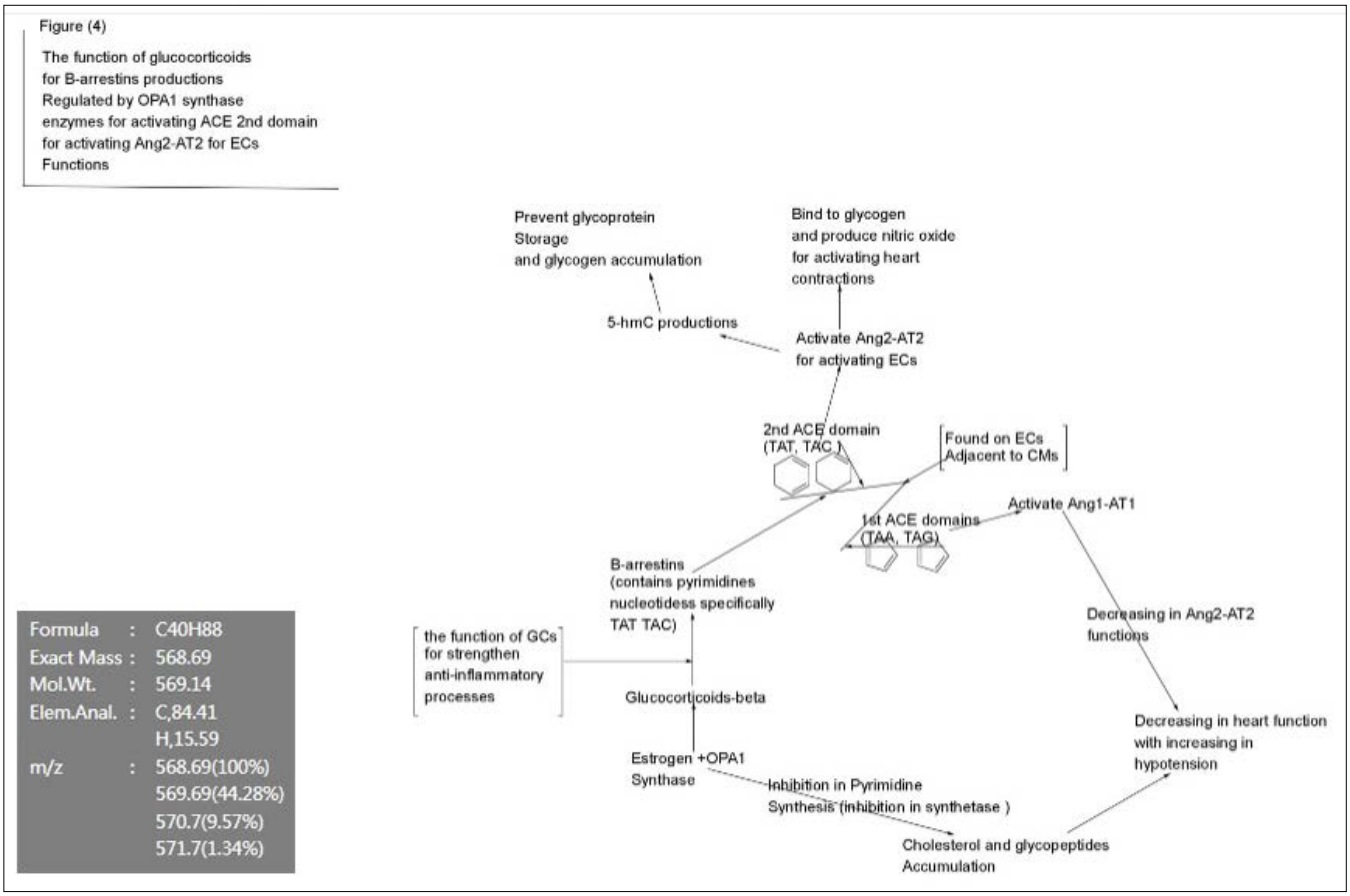

Figure 4

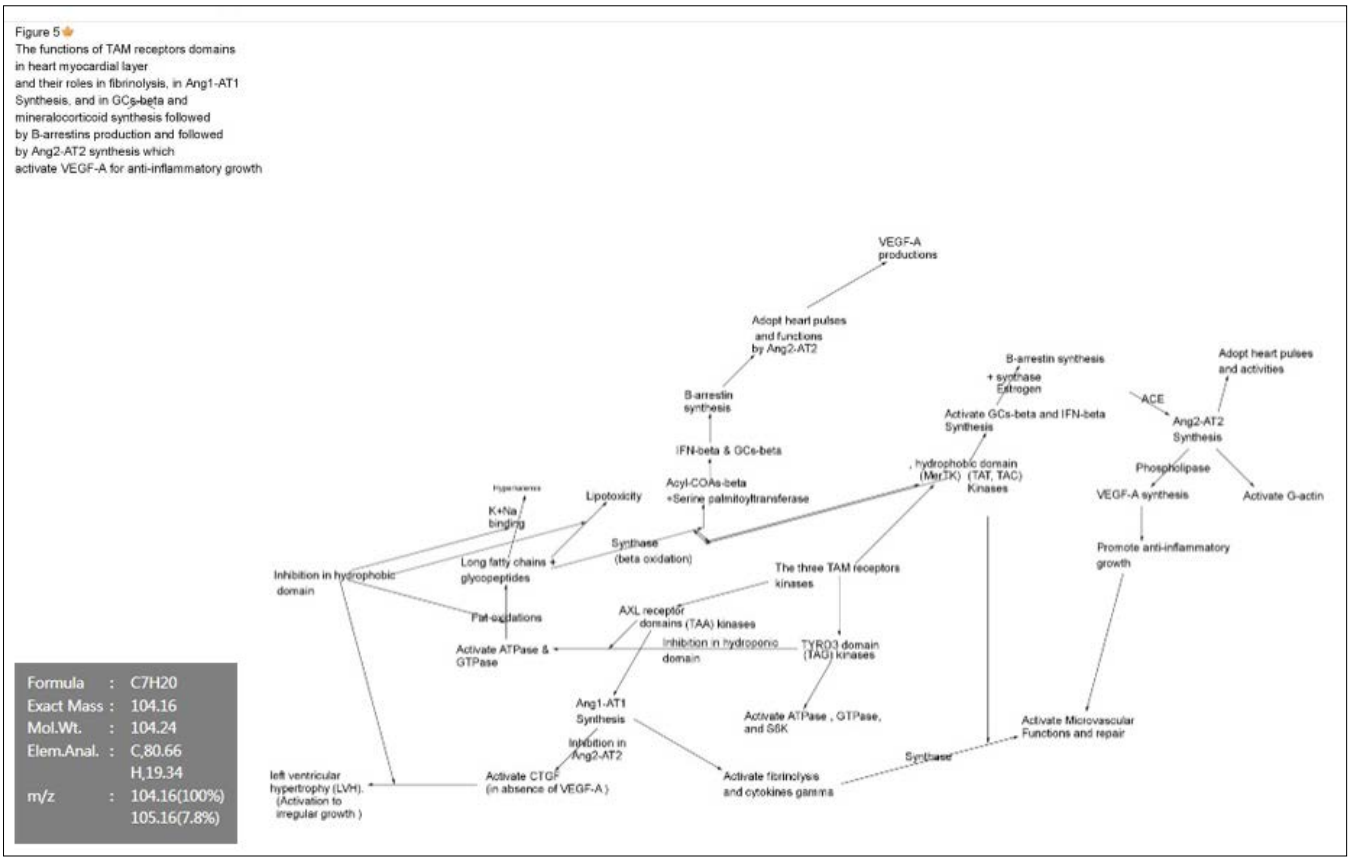

Figure 5

Methods and Results

Glucocorticoids (GCs) are steroid hormones (member of the nuclear receptor (NR) family of intracellular receptors) that contains the estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), and mineralocorticoid receptor "MR" as well as several orphan receptors are involved in cardiac function, reproduction and (embryonic) development, and the immune system [1].

Where orphan beta receptors (RORs pathway) are necessary for Estrogen synthesis (that cholesterol is the substrate for Estrogen synthesis) and consequently for Acyl-COA-beta synthesis which promote IFN-beta and GC-beta synthesis necessary for B-arrestin productions (which known as adaptor protein) that activate ACE functions for Ang2-AT2 synthesis and followed by VEGF-A synthesis for adopting anti-inflammatory growth.

That it looks to me that pyrimidine kinases, estrogen, and glucocorticoid-beta are the basis for regulating all cardiac endothelial proper developments and functions includes Cardiomyocytes and endothelial cells activities that consequently are Regulated by tyrosine TAT and TAC kinases, and by fatty-Acyl-COA-beta productions which regulated by OPA1 enzymes, and by hydrophobic amino acids synthesis which regulated by Proline amino acids functions (and the amino acids synthesis promoted by pyrimidine synthesis which regulated by OPA1 synthetase functions).

The development of Cardiomyocytes cells depend on endothelial cells functions which controlled by B-arrestins which adopt ACE that located on the surface of endothelial cells for adopting Ang2-AT2 synthesis for adopting heart activities and constrictions followed by activating VEGF-A necessary for anti-inflammatory growth.

That in mammalian myocardium, each Cardiomyocyte is surrounded by an intricate network of capillaries and is next to endothelial cells , where the Endothelial Cells Guide Cardiomyocytes, that it's clear that endothelial cells system in cardiac morphogenesis play important roles and most likely also in survival and function of mature Cardiomyocytes [2].

So, ACE is located on endothelial cells surface in Myocardial layer to activate ECs through producing Ang2-AT2 and also adopte and guide CMs activities, that ACE are stimulated and activated by the adaptor B-arrestins production (which basically regulated by glucocorticoid-beta and Estrogen synthesis) myocardial layer. That in Myocardium layer the Mineralocorticoids (which originally found in glucocorticoids molecules) are playing its important roles for getting rid of K and Na binding molecules, and in the same myocardial layer the purines which represented as glycopeptides and Ang1-AT1 will be moved to endocardial layer then to blood stream.

The Mineralocorticoids will bind to K and Na then will be migrated to epicardium layer for getting rid of the Na and K binding molecules which can cause Hyperkalemia and hardening to heart layers and blood vessels.

Notice that "The adrenal glands in a newborn baby are much larger as a proportion of the body size than in an adult" For example, at age of three months the glands are four times bigger in size than kidneys. The size of the glands decreases relatively after birth and after decreasing in liquid dairy feeding.

That GCs are mainly synthesized in the cortex of adrenal glands (and represents the main source for strength immune function), where the cortex of adrenal glands consist of three layers

- The outer zona glomerulosa (which produce Mineralocorticoids (such as aldosterone)), the middle zona fasciculate (which produce glucocorticoids),
- And the inner zona reticularis (that produce androgen).

The same composition of adrenal glands are found in heart muscles layers which consist of

- Epicardium layer which contains Mineralocorticoids for running its function for bind ro K and Na then migrate to kidney,
- Myocardial layer which contains glucocorticoids and B-arrestins that have important roles for activating ACE for Ang2-AT2 which necessary for adopting heart pulses and functions,
- And Endocardium layer which contains extra purines and glycoprotein in the forms of Ang1-AT1 that can be directed to blood stream for reactivating ATPase, and GTPase which necessary for brain activities and reactivating OPA1 membranes.

It's true that Cholesterol synthesis (due to fat digestion) which are the important substrate for Estrogen synthesis upon synthase function which promote glucocorticoid-beta synthesis throughout nuclear orphan pathways followed by B-arrestins synthesis, But androgens are formed from Thr "ACG, ACA, ACC " phosphorylation in mTOR pathway that are converted to fully functional sex hormones in the gonads and other target organs, that Threonine "Thr" phosphorylation enhance purines kinases synthesis and S6K production , and the glycoprotein with glycopeptides Production but Thr can not enhance building active promoter in IFN-beta, in GC-beta, in B-arrestins and in Ang2-AT2 molecules, that the pyrimidine TAT and TAC kinases synthesis are having the responsibility for building promoters in active beta subunits , that pyrimidine synthesis regulated by synthetase functions. That the decreasing in synthetase and consequently in Proline, Ser, Leu, and tyrosine synthesis will convert the mineralocorticoid from agonist to antagonist response that can be the reason for increasing the k and Na binding toxicity in heart layers with reduction in adopting heart functions.

So, the hydrophobic domain in TAM receptors kinases are playing important roles in protecting mineralocorticoid in agonist response. That in absence of Ser and Leu with availability of Thr amino acids can convert the agonist characters of MR to be antagonist when replace leucine in mineralocorticoid molecules.

Where, it has been reported that, Substitution of a leucine by threonine in helix 8 of the ligand-binding domain of the zebrafish MR confers the antagonist response [3]. The antagonist means when mineralocorticoid "MR" used as drugs they bind to the target receptor but do not produce a response).

That also, availability of Asp, Glu in mineralocorticoid are so imp which due translations will produce Leu in "MR" molecules that will confer agonist functions

GAC "Asp" <¬>CTG "IL"
GAA "Glu"¬¬¬-translations -->CTT Leu
GAG "Glu" ¬¬> CTC "Leu"

The Tyr, Leu, Ser, Île, Asp amino acids when contained in specific biological molecules can protect their agonist response. Threonine amino acids promote androgen through phosphorylation process which can produce purines kinases through mTOR pathway that when purines kinases exceeded with decreasing in pyrimidine kinases will reflect increasing in androgyne with decreasing in estrogen with decreasing in mineralocorticoid that will lead to decreasing in preventing K and Na binding molecules and lead to Hyperkalemia.

The myocardial layer is considered as the main important muscle layer in heart that responsible for creating and adjusting the heart contractions and control both CMs and ECs activities through the ACE functions and B-arrestins functions for activating Ang2-AT2 synthesis from Ang1-AT1.

The middle myocardial layer contains the Acyl-COA beta which are the main for activating endothelial cells through glucocorticoids-beta synthesis which necessary for B-arrestins synthesis (upon availability of estrogen) which responsible for activating Ang2-AT2 production.

The inner endocardial layer contains the free purine kinases and Ang1-AT1 that released from myocardial layer that will migrate to blood stream for activating both ATPase and GTPase for cellular activities. In myocardial layer The potassium and sodium will be separated from the received blood throughout their binding to mineralocorticoid then migrating to epicardium layer then to kidney and skins pores. While at the same time glucocorticoids-beta will produce B-arrestins for adjusting the heart-beats and for activating ACE functions for Ang2-AT2 productions from the excess of Ang1-AT1 (the free Ang1-AT1 will migrate to endocardial layer then to blood stream for activating ATPase, GTPase, and for CTGF productions).

The B-arrestins synthesis can be produced and then activate ACE within the myocardium layer, while the Acyl-COA-beta can be activated in the myocardium upon synthase function for reactivating the GC-beta and mineralocorticoid "MR", that MR can bind to Na and to K for adjusting the pH and protecting heart muscles from hardening and from Hyperkalemia then will migrate to Epicardium layer for migrating to skins pores and kidney.

Glucocorticoids and then mineralocorticoid are so important to get rid of the extra purines and the K and Na binding molecules and then migration to epicardial layer then to kidney which necessary for protecting heart from the danger of K and Na binding molecules.

The heterogenous cells (which originated from proepicardial in embryo early stages are so imp for Acyl-COA-beta production which promote GCs and IFN-beta productions for protecting heart functions and activities. Peroxiredoxin contains cytosine kinase "TAC kinases" for adopting and protecting estrogen for B-arrestin

Synthesis

The Peroxiredoxin 1 productions are so necessary for protecting estrogen [4]. That, The peroxiredoxins is mainly based on their unique active center cysteine with a wide range of redox states and the ability to switch between low- and high-molecular-weight species for regulating their peroxidase and chaperone activities [5].

As estrogen synthesis promoted by pyrimidine kinases synthesis as the Peroxiredoxin are also regulated by pyrimidine TAT and TAC kinases for protecting both estrogen synthesis and B-arrestins synthesis through orphan beta oxidative pathway, that cytosine kinase (TAC kinases) has the roles to adopt and switch between low- and high-molecular-weight species for activating their peroxidase functions for cooperation and protection the estrogen which necessary for B-arrestin synthesis (so peroxiredoxin important to regulate B-arrestins synthesis).

That B-arrestins synthesis (regulated by both estrogen and glucocorticoid-beta which mediated by Acyl-COA-beta synthesis upon synthase effect) are so important adopting Ang2-AT2 synthesis through firstly activating ACE functions for adopting Ang2-AT2 from Ang1-AT1 for adjusting heartbeat , that Ang2-AT2 necessary for regulating VEGF-A, production for activating both CMs and ECs growth and repair, Where, Endothelial Cells Express VEGF via TLR4 [6]. So, Ser phosphorylation for producing the protein of thymine kinases and protein of cytosine kinases are the basis for promoting Peroxiredoxin 1 synthesis which adopt and protect B-arrestins synthesis (that adopt and protect estrogen), that estrogen basically regulated by pyrimidine kinases and synthase effect on cholesterol and on Acyl-COA-gamma that necessary for producing Acyl-COA-beta), that we can consider that pyrimidine kinases and peroxiredoxin 1 (PRDX 1) are necessary for ACE to adopt Ang2-AT2 productions and running adopted angiogenesis, and PRDX1 play basics roles in protecting and adopting heart pulses in proper conditions.

The contractions and relaxation activated by phosphorylation whether by ATPase "false constriction" and by pyrimidine kinases functions "real proper constriction" that each of proper pulse is reflecting the released energy units from phosphorylation process through that pyrimidine TAT and TAC kinases and OPA1 synthase to regulate the activation of estrogen, Acyl-COA-beta, GC-beta, PLCγ2, IFN-beta, and B-arrestins synthesis which activate ACE (which placed on endothelial cells) for adopting Ang2-AT2 synthesis from Ang1-AT1 for protecting heart and adjusting heart functions and pulses, that pyrimidine kinases are the basis for improving and adopting heart pulses and activities.

The epicardium layer responsible for reactivating the mineralocorticoid to bind with K and Na in Myometrial layer for migrating to epicardium then to kidney and skins pores far from myocardial functions for proper maximum rate of construction, but the inner layer will migrate the free purines kivases "Ang1-AT1" from the ACE functions (for Ang2-AT2 synthesis) to blood stream for ATP and GTP activities, and for activating brain functions which depends on hydrophobic domain (MerTK domain) functions in the TAM receptor kinases.

Atherosclerosis defined as accumulation in long fatty chains and cholesterol (deficiency in estrogen synthesis and in peroxiredoxin 1) that may bind to K and Na salts and can lead to Hyperkalemia toxicity in heart layers associated with reduction in glucocorticoid-beta and then reduction in B-arrestin productions , therefore Acyl-COA gamma and the long fatty acids chains need to be enrolled for fatty Acyl-COA-beta production followed by GC-beta and IFN-beta synthesis for promoting B-arristin and followed by Ang2-AT2 synthesis.

Atherosclerosis can reflect deficiency in ROR beta pathway too due to inhibition in synthase function, that will cause accumulation in Gamma subunits (Acyl-COA gamma) followed by cholesterol acclamations in blood vessels with decreasing in GC-beta and in B-arrestins production , and also will lead to increasing in Ang1-

AT1 (due to decreasing in Ang2-AT2) that will lead to increasing in GPRCs and in AXL membrane (which characterized by purines kinases) that can improve the increasing in left vertical size (due to decreasing in the VEGF-A production which regulated by Ang2-AT2 productions).

That it has been reported that B-arrestins proteins play a well established role in the dampening of G-protein coupled receptor (GPCR) signaling [7].

The B-arrestins has the adaptive role in dampening G-protein coupled receptor (GPCR) that prevent GPCRs accumulation and prevent serious cardiac diseases as increasing in left vertical size, and prevent Atherosclerosis through adopting the Recruit of Gps which simplify in Ang2-AT2 synthesis (from Ang1-AT1) through activating ACE domains which appear in the proper improvements of both of CMs and endothelial cells functions through creating and adjusting and protecting the heart pulses.

Proper mineralocorticoid and B-arrestins are necessary for protecting heart from "Hyperkalemia and from hypertrophy" adopted by pyrimidine TAT and TAC.

Kinases

Endothelial cells are the basis of Myocardial layer that have ACE on their surface for adopting myocardial functions through Ang2-AT2 synthesis that controlled and adopted by B-arrestins synthesis, where B-arrestins produced by glucocorticoid-beta and Estrogen upon synthase functions for adopting and protecting heart layers functions throughout repairing aldosterone and mineralocorticoid [8].

Where mineralocorticoids are cooperating in the increasing in anti-inflammatory pathways through binding to K and Na then migrate to epicardium layer then to kidney for protecting heart layers. That glucocorticoid-beta and B-arrestins in the myocardial layer are always in order (upon availability of pyrimidine kinases and Acyl-COA-beta biosynthesis) for producing mineralocorticoid for protecting heart from K and Na binding molecules. That it's clear that pyrimidine TAT and TAC kinases and orphan nuclear pathway promote B-arrestins and mineralocorticoid synthesis (through GCs beta and Estrogen synthesis) for strengthen anti-inflammatory processes and protecting heart layers from accumulated GPCRs, from Hyperkalemia , and from the formation of lipotoxicity.

Glucocorticoid-beta and mineralocorticoids are basically regulated by tyrosine TAT and TAC kinases (Pyrimidine kinases) for protecting heart from Hyperkalemia, and for strengthen their roots in B-arrestins synthesis regulated by estrogen , that B-arrestins will adopt "and stimulate" ACE activities which located on endothelial cells in for adopting both CMs and ECs functions throughout Ang2-AT2 synthesis which protect and adjust heart contractions and activities followed by adopting VEGF-A synthesis and G-actins activations which necessary for reactivating heart function and angiogenesis pathways, and anti-inflammatory growth.

That, Mineralocorticoid and Estrogen Receptors in Endothelial Cells Coordinately Regulate Microvascular Functions [9].

That, Mineralocorticoid and Estrogen Receptors in Endothelial Cells Coordinately Regulate Microvascular Functions So, Peroxiredoxin 1 also regulate and protect both estrogen and B-arrestins synthesis for Ang2-AT2 synthesis which necessary for VEGF-A synthesis for adopting microvascular repair and anti-inflammatory growth.

VEGF is also able to activate heterologously expressed TRPC3/6 channels through VEGFR2 [10]. So, Vascular endothelial growth factor (VEGF) (adopted by Ang2-AT2 functions) has its strong basis roles for activating and protecting human microvascular endothelial cells (HMVECs) activities and functions which mainly regulated and protected by peroxiredoxin 1 which protect both Estrogen and B-arrestins followed by Ang2-AT2 synthesis for promoting anti-inflammatory growth via VEGF-A productions.

Glucocorticoid-beta and Estrogen Receptors are so important for producing B-arrestin (throughout peroxiredoxin 1 protection to estrogen synthesis) in Endothelial myocardial layer for regulating and activating ACE which placed particularly on ECs for promoting Ang2-AT2 from Ang1-AT1 then followed by activating the VEGF-A productions for running anti-inflammatory growth for adopting microvascular functions.

The mineralocorticoid are necessary for protecting heart from Hyperkalemia and from Hypertrophic cardiomyopathy (HCM) which defined as the heart muscle becomes thickened (hypertrophied) due to increasing in the long fatty chains and glycopeptides with high Molecular weight bind with one or more salts which associated with decreasing in the necessary pyrimidine kinases and decreasing in GC-beta and in B-arrestins synthesis.

The high sodium and potassium accumulation can increase hardening and toxicity to left ventricular hypertrophy (LVH) through binding to cholesterol and to the accumulated glycopeptides and glycoprotein which activate CTGF synthesis for irregular growth. That it has been reported that, sodium has a direct effect to induce cellular hypertrophy and may therefore be an important determinant in causing myocardial and/or vascular hypertrophy in subjects with increased sodium concentration [11]. The Hypertrophic cardiomyopathy (HCM) is a disease that causes heart muscle to enlarge (hypertrophy) with hardening, mediated by increasing in the uncontrolled CTGF productions (which promoted by the accumulated GPCRs activities with decreasing in VEGF-A productions which depend on Ang2-AT2 productions).

In immune cells, the interaction of GCs with the endothelial cell plasma membrane (where ACE located on the endothelial cell plasma membrane) plays a critical roles in rapidly reducing the K and Na binding molecules across the membranes through the rapidly mineralocorticoid synthesis which bind to K and Na salts then migrated to epicardium for migrating the toxic salted molecules far from heart muscle (to get rid of K and Na molecules) to kidney and skins pores.

The Epicardium and myocardial layers are characterized by high cellular plasticity that are playing important roles in converting cholesterol to estrogen through the effects of synthase on cholesterol (and on long fatty chains by synthetase to produce Acyl-COA-gamma followed by synthase for Estrogen synthesis and Acyl-COA-beta synthesis) to produce a estrogen followed by fatty Acyl-COA-beta which promote GC-beta for promoting B-arristin which has the role of activating ACE for Ang2-AT2 synthesis for promoting VEGF-A productions for adopting microvascular repair and anti-inflammatory growth.

The heterogenous cells population that composes the epicardium originated primarily from a transient embryonic cell cluster known as the proepicardial organ (PE) Characterized by its high cellular plasticity [12].

The pro-epicardial and myocardial epithelial cells are cooperate for proper protection and proper improvement to heart function via the activation of acyl-CoA-beta (promoted by the hydrophobic domain in TAM receptors kinases) which activate Serine palmitoyltransferase that has the roles of activating both GCs-beta and IFN-beta for promoting B-arrestins in Myocardial layer that consequently inhibit Ang2-AT2 and VEGF-A productions. Mineralocorticoid prevent lipotoxicity and Hypertrophic cardiomyopathy for keeping the vitality of the heart muscles, and for protecting the Ang2-AT2 and VEGF-A synthesis.

Increasing in heart vitality will be followed by adjusting the purines kinases percentage (which suppose to be adopted by ACE functions through Ang2-AT2) that the free glycoprotein can be moved to inner endocardial layer then to blood stream.

The more sodium and potassium accumulation in Myocardial layer can bind to long fatty chains and cholesterol (which have high affinity to bind with those danger salts promising high stability) followed by decreasing or inhibition in glucocorticoid-beta Biosynthesis lead to inhibition in B-arrestins and decreasing or inhibition in ACE functions with increasing in Ang1-AT1 and in GPCRs activities.

That inhibition in ACE will inhibit Ang2-AT2 synthesis followed by increasing in glycoprotein accumulations and in Ang1-AT1 associated with increasing in ATPase and GTPase activities followed by increasing in long fatty chains that can lead to increasing in oxygen rich carbon synthesis and in Oligomycin synthesis in vivo which increase the binding of affinity to K and Na salts followed by Hyperkalemia (notice oligomycin will inhibit synthase function followed by inhibition in estrogen synthesis and associated with cholesterol accumulations).

Where, it has been reported that: The Hyperkalemia associated with use of angiotensin-converting enzyme "ACE" inhibitors and angiotensin receptor blockers [13].

So now it's important to recognize "it's forbidden to inhibit ACE functions" that will be the result of raising the potassium accumulation in blood (that cause toxicities) and will be associated with reduction or inhibition in Ang2-AT2 productions that will be result of accumulation in the glycoproteins and glycopeptides in blood with increasing in CTGF that will lead to increasing in left vertical size and associated with clogged arteries that will lead to hypotension and heart failure.

Also, Heart failure associated with inhibitions in tyrosine TAT and TAC kinases which inhibit both GC-beta and B-arrestins synthesis followed by inhibition in adopting ACE functions and in Ang2-AT2 synthesis then followed by inhibition in VEGF-A functions that will associated with accumulation in long fatty-chains which have high affinity to bind with k and Na that can lead to lipotoxicity or Atherosclerosis (depending on type of binding salts, it's concentration and types of its binding molecules and their molecular weights) with increasing in the irregular endothelial growth through CTGF productions that will cause increasing in left vertical growth that can cause hypotension followed by heart failure.

That it has been reported that: Heart failure associated with small molecule tyrosine kinase inhibitors [14].

Direct feeding with B-arrestins and Ang2-AT2 to Epicardia and myocardial layers necessary for treating the Cardiac tamponade Or Pericardial effusion (PEff): Pericardial effusion (PEff) is defined by an increasing in the physiological amount of fluid within pericardial space. It can appear followed different medical conditions, mainly related to inflammations and cardiac surgery.

Cardiac tamponade is a critical condition that occurs after sudden and/or excessive accumulation of fluid in the pericardial space (that due to Brocken endothelial cells which due to increasing in inflammatory molecules with decreasing in IFN-beta and GCs-beta synthesis) that restricts appropriate filling of the cardiac chambers disturbing normal hemodynamics and ultimately causing hypotension and cardiac arrest [15].

The excessive accumulation of fluid in the pericardial space is expected due to Brocken heterogenous cells in epicardia layer that their repair need to reactivate adopted VEGF-A synthesis by reactivating both of B-arrestins followed by Ang2-AT2 synthesis.

The glucocorticoid-beta treatment to the myocardial layer after surgery (or due to accumulations of inflammations) also will accelerate IFN-beta and B-arrestins Synthesis that will protect and prevent accumulated long fatty chains and will prevent K and Na binding molecules, and will accelerate the Ang2AT2 synthesis for promoting VEGF-A productions which will promote anti-inflammatory growth processes (for repeating Brocken tissue) and microvascular repair and functions.

Also, Glucocorticoid-beta in Myocardial layer (promoted by fatty Acyl-COA-beta synthesis upon synthase functions) will promote the Ang2-AT2 synthesis (through B-arrestins productions which stimulate ACE functions) which adopt heart pulses and activities followed by Vascular Endothelial Growth Factor Expression (VEGF-A) productions necessary for the adopted anti-inflammatory growth. That, Ginsenoside-Rg1 Induces Vascular Endothelial Growth Factor Expression through the Glucocorticoid Receptor-related Phosphatidylinositol 3-Kinase/Akt and β-Catenin/T-cell Factor-dependent Pathway in Human Endothelial Cells [16].

And also, the estrogen (which involved in B-arrestins biosynthesis and regulated and protected by peroxiredoxin 2) are important regulatory tool for VEGF-A activities in adipose tissue repair. That it has been reported that Estrogen receptor 1 (ESR1) regulates VEGFA in adipose tissue [17].

So, Estrogen receptor 1 (ESR1) (which necessary for the adopting B-arrestin synthesis) are necessary for activating ACE for adopting both the Ang2-AT2 synthesis and VEGFA production in adipose tissue (throughout B-arrestins synthesis) for adjusting VEGF-A for the regulated anti-inflammatory growth.

Endocardial Layer Include Fibrinolysis Adopted by B-Arrestins Which Adopt Ace and Ang2-At2 Productions in Myocardial

The fibrinolysis promoted by both AXL and Tyro3 domains contained in TAM receptors three domains, where, inhibition in MerTK receptor domain in TAM receptors will lead to the increasing in AXLs (TAA TAG kinases) level which promote the increasing in ATPase functions associated with decreasing in Ang2-AT2 and in VEGF-A productions (which necessary for anti-inflammatory growth and microvascular repair and functions).

The MerTK receptor domain in TAM receptors is tyrosine TAT and TAC kinases which necessary to promote both of IFN-beta and glucocorticoid-beta which regulate B-arrestins productions which consequently will adopt and stimulate ACE for Ang2-AT2 and VEGF-A for anti-inflammatory growth including microvascular repair and reactivation properly. Note, there adopted balance between "Axl, TYRO3 domains " and MerTK domain that as decreasing in MerTK domain related to other two domains will increase fibrinolysis with decreasing in GC-beta and in VEGF-A productions.

Where, Both IFN-α and IFN-β block VEGF-induced angiogenesis, that IFN-β is more effective than IFN-α in disrupting the fibrinolysis system [18].

The IFN-beta
(GCs-beta
<¬>IFN-beta) are more contributing in the recruitment of thromboxane-A Biosynthesis through promoting Ang2-AT2 synthesis from Ang1-AT1 followed by VEGF-A for microvascular repair and reactivation (imp notes that B-arrestins bind to stored glycogen for activating ACE on cells surface to promote Ang2-AT2 synthesis from Ang1-AT1 with metalloproteinase dependent for platelets activation mediated by releasing nitric oxide).

G-protein receptors ratio (G-protein promote thrombomodulin through Ang2-AT2 synthesis from Ang1-AT1 upon ACE functions) are adopted by B-arrestins for protecting VEGF-A productions necessary for adopting blood flow where, increasing in Ang1-AT1 Biosynthesis will promote fibrinolysis, but increasing in Ang2-AT2 will adopt VEGF-A synthesis and TXA2 synthesis.

The GPR15 plays an important role in mediating cytoprotective function as well as Thrombomodulin "TM" [19]. That, G-protein receptors act as receptor for Ang2-AT2 synthesis upon ACE functions and mediated by B-arrestins function for Thrombomodulin production.

Thrombomodulin is an endothelial cell surface molecule that plays an essential role as a cofactor in the thrombin-mediated activation of protein C, an anticoagulant protein, as well as thrombin-activatable fibrinolysis inhibitor (TAFI) [20]. That thrombomodulin acts as a cofactor of thrombin-catalyzed activation of protein C that inhibits the procoagulant functions of thrombin.

The Hemophilia can be explained as decreasing in Tyr TAT and TAC kinases (with increasing in TAA and TAG kinases) that can reflect decreasing in both GCs-beta and in B-arrestins and consequently followed by decreasing in Ang2-AT2 and in microvascular functions (decreasing in VEGF-A productions which regulated by Ang2-AT2 synthesis) associated with increasing in fibrinolysis .

That it has been reported that Lactate engaged the PI3K/Akt pathway via ligand-mediated activation of the three receptor tyrosine kinases Axl, Tie2, and VEGF receptor 2 [21].

Firstly lactate (lactic acid) stimulate increasing in phosphorylation by ATPase and synthetase for producing purines kinases (engagement to AXL and FN domaine synthesis) and pyrimidine kinases (engagement to hydrophobic domain (in TAM receptors) necessary for GC-beta and IFN-beta synthesis.

That the Lactate-driven activation of PI3K/Akt is not dependent on Axl, Tie2, and VEGFR-2 A, but the Axl, Tie2, and VEGFR-2 A, synthesis dependent on lactate metabolic pathways regulated by ATPase function followed by synthetase functions then synthase for Acyl-COA-beta synthesis for GCs-beta and IFNbeta synthesis necessary for Ang2-AT2 synthesis followed by VEGF-A synthesis. And the Conclusion of that article is the lactate stimulate Akt and S6K productions through stimulating purines and pyrimidine kinases synthesis upon Ser /Thr phosphorylation (include synthetase functions) in mTOR pathway, where purines kinases necessary for AXL and Tie2 synthesis (the two first domains in TAM receptors kinases) which are necessary for Ang1-AT1 synthesis, while pyrimidine kinases produced by Ser phosphorylation are necessary for hydrophobic domain (MerTK domains) in TAM receptors kinases which responsible for activating IFN-beta GCs-beta (upon synthase effect on AcylCOA-gamma subunits) for promoting B-arristin necessary for adopting Ang2-AT2 synthesis through the function of ACE (which located on endothelial cells functions) followed by VEGF-A synthesis necessary for anti-inflammatory growth for re-adopting microvascular activities [22].

Also, Rac1 has the roles of activating IFN-beta and GC-beta which promote both B-arrestins and Ang2-AT2 synthesis and activities. That, it has been reported that , the Rac1-Mediated Activation of Mineralocorticoid Receptor [23].

The Rac1 has expand its roles for its importance in mediating glucocorticoid-beta (GCs-beta) and mineralocorticoid synthesis (where, rac1 and GC-beta regulated by pyrimidine TAT and TAC kinases) that as Rac1 mediate mineralocorticoid productions, as indicated its roles in mediating the GCs-beta synthesis followed by B-arrestins synthesis in cardiac layers (in Myocardial layer), so indicate that Rac1 has basic roles in adopting ACE (which adopt GPCRs ratio and glucose uptake to skeletal muscle) for Ang2-AT2 synthesis for adopting heart functions and constriction (that active Rac1 activities has functions of protecting the adopted contraction-stimulated skeletal muscle) followed by VEGF-A synthesis in Myocardial heart layer. That, AMPK/Axin1-Rac1 signaling pathway mediates contraction-stimulated skeletal muscle glucose uptake [24].

So, it's clear that Rac1 activation play important roles in cardiac layers functions through mediating mineralocorticoid productions and through reactivating GC-beta followed by B-arrestins and then Ang2-AT2 synthesis (which appeared as adopt glucose uptake in skeletal muscle cells that consequently adopt the GPCRs ratio through mediating the B-arrestins synthesis which bind to GPCRs then delivered to ECs surfaces for stimulating ACE for activating Ang2-AT2 synthesis from Ang1-AT1 (prevent increasing in GPCRs and in Ang1-AT1) necessary for activating VEGF-A synthesis for microvascular functions and anti-inflammatory growth (so activations proper Rac1 has the importance role in adopting VEGF-A productions and anti-inflammatory growth).

That, Rac1 activate endothelial functions and activate CMs functions mediated by PLCγ2 and IFN-beta synthesis for TXA2 synthesis for strengthen anti-inflammatory processes for the long cells survival that will be mediated by adjusting and preventing hyperglycemia [25, 26]. That, B-arrestin-1 dependent signaling pathway for p38 mitogen-activated protein kinase activation by beta2-adrenergic receptors [27].

That Rac1 rich Proline activate hydrophobic acids synthesis (regulated by pyrimidine TAT TAC kinases) which activate IFNbeta and GC-beta (mediated by MAPK function and by synthase for Acyl-COA-beta synthesis) that activate B-arrestins synthesis which adopt the glycoprotein ratio through binding to GPCR-B for stimulating ACE and for Ang2-AT2 synthesis (from Ang1-AT1) which protect and adopt heart layers activities, and also promote VEGF-A synthesis for adopting microvascular functions.

So, there are a strong correlation between RAC1 and B-arrestins production in protecting heart functions and in the regulation of microvascular functions and growth . I would like to note that the rules of GCs-beta in fibrinolysis is the adjusting Ang1-AT1 ratio by adopting Ang2-AT2 synthesis through B-arrestins synthesis which stimulate ACE functions (the switch key) to reduce the increasing in Ang1AT1 throughout Ang2-AT2 productions followed by VEGF-A synthesis for activating anti-inflammatory growth which adopt microvascular activities.

But due to decreasing in GCs-beta production the Ang1AT1 synthesis will be increased (followed by production in "Thrombomodulin modulations by B-arrestins) which promoted by G-protein receptors and Ang1-AT1 productions that will lead to activate CTGF productions which activate irregular (un-adopted) growth (in absence of VEGF-A which promoted by Ang2-AT2 productions).

The necessity of pyrimidine kinases (TAT and TAC) in Acyl-COA-beta for B-arrestins synthesis for preventing cardiac toxicity and Ventricular fibrillation

OPA1 synthase regulate ROR-beta productions pathway where RORs are fully connected to significantly regulated by RTKs too (where RTKs were found to be activated in expression in ischemic heart) that ROR1 and R-Tyrosine Kinases are a potential target for the treatment of ischemic heart injury.

Where, ROR beta productions are a fatty Acyl-COA beta biological molecules (which regulated by pyrimidine "TAT and TAC" kinases and synthase) that produced upon the OPA1-synthase effect on fatty Acyl-COA-gamma (inflammation) for improving Acyl-COA-beta synthesis then will promote both glucocorticoid-beta and IFN-beta that protects heart from coronary diseases which included the increasing in both K and Na "Hyperkalemia" that can lead to primary arrhythmia and heart attack (in cause of Deficiency in pyrimidine kinases and in Acyl-COA-beta).

That it has been reported that p38 MAPK regulates triacylglycerol Biosynthesis followed by Acyl-COA-gamma upon synthetase functions followed by Acyl-COA-beta synthesis [28]. Which followed by GCs-beta production and B-arrestins synthesis which promote Ang2-AT2 synthesis necessary for adjusting heart functions.

And, AMPK mediate lipid metabolism by Phosphorylation, Where, The α/β-adrenergic stimulation lead to AMPK activation by stimulating the upstream signaling of AMPK [29].

The role of B-cell is expanding their functions for fatty Acyl-COA beta which regulated by synthase enzyme for promoting both GC-beta and IFN-beta which are necessary for protecting myocardial functions through GCs-beta and mineralocorticoid synthesis and for B-arrestins synthesis.

That, the activated B cells expand their pool of acetyl-CoA, which is likely dependent on the activity of ATP-citrate lyase (ACLY) 12 [30]. G-protein can be regulated and promoted by both S6K and Ser /Thr phosphorylation involved in mTOR pathway which produce both pyrimidine kinases and purines kinases (that purines kinases promote Ang1-AT1 and "Gp-receptor"), that pyrimidine kinases promote GC-beta upon synthase functions necessary for B-arrestins synthesis which prevent GPCRs accumulation through stimulating ACE for adopting Ang2-AT2 synthesis from the excess of Ang1-AT1 for promoting anti-inflammatory growth.

Also , Ang2-AT2 synthesis associated with active signals which necessary for creating and adjusting heart pulses and running active necessary angiogenesis pathways and those active signals are the main for adopting heart beats and functions . B-arrestins also can still remain stable after binding to GPCRs and drive it for stimulating ACE at cells surface for activating Ang2-AT2 productions from Ang1-AT1 for protecting myocardial activities and heart functions.

That it has been reported that, that β-arrestins remain active after dissociation from receptors, allowing them to remain at the cell surface and presumably signal independently [31].

Also, The nucleocytosolic acetyl-CoA alpha are a signature of a "growth pathway" due to the effect of Phospholipase on Acyl-COA-beta for promoting TLR4 and SIRPα1 necessary for anti-inflammatory growth. The tyrosine TAA and TAG kinases and S6K are basically for regulating the nucleocytosolic acetylCoAs (acetyl-CoA-alpha upon phosphorylase effect on proper Acyl-COA-beta which included in Ang2-AT2 synthesis and in VEGF-A molecules) Biosynthesis which upon the synthase effect on Acyl-COA gamma will (the effect of ATPase on fats will produce long fatty chains followed by synthetase effect for AcylCOA-gsmma synthesis) produce Acyl-COA-beta followed by B-arrestins synthesis then Ang2-AT2 synthesis which promote VEGF-A productions then followed by phospholipase effects for activating nucleocytosolic acetyl-CoA-alpha productions which activate the anti-inflammatory growth.

Where, it has been reported that High nucleocytosolic acetyl-CoA amounts are a signature of a "growth" or "fed" state and promote its utilization for lipid synthesis and histone acetylation [32].

That as nucleocytosolic acetyl-CoA alpha activated due to lipid metabolism for producing Acyl-COA-beta upon synthase function for GCs-beta and IFN-beta synthesis followed by B-arrestins synthesis necessary for Ang2-AT2 synthesis and nucleocytosolic acetyl-CoA alpha, as VEGF-A, and nucleocytosolic acetyl-CoA alpha, as nucleocytosolic Acyl-COA alpha are the most necessary improved steps regulated by VEGF-A productions for anti-inflammatory growth and cells improvements.

As the synthesis of Acyl-COAs In embryo are promoting the nucleocytosolic acetyl-CoA-alpha productions as the nucleocytosolic alpha (NSO-alpha) is the main important improved steps for anti-inflammatory growth started is activity early in embryo, that the NSO-alpha regulated firstly by GC-beta followed by B-arrestins productions then followed by Ang2-AT2 synthesis necessary for adopting microvascular functions by VEGF-A synthesis which promote nucleocytosolic acetyl-CoA-alpha synthesis necessary for anti-inflammatory growth and microvascular functional improvement.

The activation of angiogenesis through ACE activities will adopt the Ang2-AT2 synthesis for VEGF-A synthesis which will promote nucleocytosolic acetyl-CoA alpha productions which can considered as an important adopter key for anti-inflammatory growth (mainly adopted by Tyr TAT and TAC followed by B-arrestins and by Ang2-AT2 synthesis) associated with extracellular and intracellular signals which adopt muscles constriction and adopt heart functions. That, tyrosine kinases can mediate transduction of both extracellular and intracellular signals [33].

Where , Both the PC tyrosine (TAT and TAC) kinases effect and angiotensin II-induced protection and are necessary for trigger mechanism of ischemic preconditioning [34]. And, the Src kinase activation mediates ischemic injury but triggers IPC in the position either upstream of or parallel to membrane-associated PKC-ε [35].

So, pyrimidines TAT and TAC kinases are so necessary for inducing protection and for trigger mechanism of ischemic preconditioning (through promoting B-arristin and Ang2-AT2 for VEGF-A productions for nucleocytosolic CoA alpha for anti-inflammatory growth) , that the protection means protections for maintaining its proper function through protection from catabolic affects by ATPase and other biological effective catabolic tools, (where purines kinase are basis for activating S6K and ATPase).

That, Src kinase (TAT kinases) activation are the trigger in ischemic injury (associated with intracellular and extracellular active signals due to pyrimidines kinases activities) which is parallel to PKC-ε (TAC kinases) activity where, PKC-ε (TAC kinases) responsible for CpG production necessary for migrating molecules, that both Src "TAT and TAC" kinases cooperating together for building specific active promoters responsible for regulate, adopt and migrate molecules (GC-beta, B-arrestins and Ang2-AT2) for recover endothelial and CMs cells activities associated with intracellular and extracellular active signals that protect and adopt heart pulses and functions.

That inhibition or sever decreasing in pyrimidine kinases synthesis (TAT and TAC kinases) activities will be associated with decreasing in the active signals produced from pyrimidines kinases which associated with their functions, that will be the result of decreasing in cardiac activities and can reflect increasing in GPCRs accumulation, lipotoxicity and Ventricular fibrillation due to increasing in the irregular CTGF growth activities (with decreasing in the VEGF-A synthesis). Where, unique cardiac toxicity profile, Ventricular fibrillation may occur as an adverse effect of tyrosine kinase inhibitors [36].

The inhibition in pyrimidine kinases means inhibition in both GCs-beta and B-arrestins followed by inhibition in both Ang2-AT2 and in VEGF-A followed inhibition in nucleocytosolic alpha productions with inhibition in anti-inflammatory growth.

Furthermore, the increasing in tyrosine kinases phosphorylation will be associated with increasing in heart pulses due to its activities which associated with active extracellular and intracellular active signals which responsible for activating, creating, and protecting heart pulses and functions then will be followed by increasing in blood flow with increasing in the intracellular calcium (means increasing in PLCγ2 function pathways) and will be associated with decreasing in K and Na binding molecules (due to GC-beta and mineralocorticoid synthesis and functions).

That it has been reported that: the increased tyrosine phosphorylation is associated with increased intracellular calcium concentration ([Ca2+]) during cell proliferation and migration [37].

The challenge roles of B-arrestins (regulated by tyrosine TAT and TAC kinases, and by both GC-beta and Estrogen proper synthesis) are so important in adopting Ang2-AT2 productions from Ang1-AT1 through stimulatibg ACE functions which located on endothelial cells mediated by GPCR-β production are prevent GPCR/G protein synthesis which called desensitization.
That it has been reported that: β-arrestins are ubiquitously expressed and function to inhibit GPCR/G protein coupling, a process called desensitization, and promote GPCR trafficking and arrestin-mediated signaling [38].

And, the B-Arrestins Participate in the Regulation of Cardiac GPCR Signaling Through Homologous and Heterologous Desensitization. And Receptor tyrosine kinases (RTK) are potential targets for the treatment of ischemic heart disease [39,40].

So, the tyrosine TAT and TAC kinases are necessary to regulate both GC-beta and its B-arrestins productions which stimulate ACE activities for adopt Ang2-AT2 productions which adjust heart beats, and promote VEGF-A which promote nucleocytosolic alpha necessary for Preconditioning ischemic injury. The receptors tyrosine TAT and TAC kinases also promote the epidermal growth factor "EGF" via RORs Pathways followed by adopted angiogenesis associated with increasing in intracellular and extracellular active signals charges that are responsible tools for increasing heart activities and functions that can increase the conductance of active constricted signals between endothelial heart layers and along arteries. That it has been reported that EGF acts via a tyrosine kinase to increase maximal I (f) conductance with no change in the voltage dependence of activation [41].

The pyrimidine kinases increase the conductance through active signals between heart and along arteries, through activating angiogenesis in myocardium layer through activating B-arrestins synthesis for ACE functions for adopting Ang2-AT2 productions, where Ang2-AT2 role is activating the regulated VEGF-A which will promote EGF for anti-inflammatory growth.

Atherosclerosis due to decreasing in tyrosine kinases (TAT and TAC), in Acyl-COA-beta (decreasing in beta oxidation) and in estrogen synthesis

Atherosclerosis is caused by a buildup of plaque in the inner lining of an artery, and can occur in heart layers. Plaque is made up of deposits of long fatty chains , cholesterol, cellular waste products, and fibrin.

Atherosclerosis due to accumulation of long fatty chains "LFC" and cholesterol (that LFC and cholesterol have high affinity to bind to salts "K and Na" cause hardening and toxicity to heart layers and to blood vessels) associated with decreasing in pyrimidine kinases synthesis, and associated by decreasing in estrogen synthesis (where estrogen Biosynthesis depends on Serine phosphorylation in mTOR phosphorylation pathways) that will lead to decreasing in Acyl-COA-beta production (with accumulation in long fatty chains and in fatty Acyl-COA-gamma) that consequently will reflect decreasing in Carnitine palmitoyltransferase-1 (CPT1) activity with decreasing or inhibition in the condensations of Serine and palmitoyl CoA (where serine palmitoyltransferase which is critical to recover cardiac lipotoxicity) both GCs-beta and B-arrestins productions.

Purines kinases which firstly produced by the Thr phosphorylation in mTOR pathway are necessary for producing S6K and glycoprotein synthesis, where the phosphorylation of Tyr (TAA and TAG) "purine" kinases will produce Ang1-AT1 which responsible for activating ATPase and CTGF productions which mediate irregular maturation and irregular proliferation (in cases of decreasing or inhibition in VEGF-A synthesis).

Where in case of absence of Tyr pyrimidine kinases (TAT and TAC) the activity of CTGF will be uncontrolled and un-adopted (which normally done through the adopter Protein B-arrestins).

The activity of B-arrestins depends on buildings dynamic active promoter (TAT and TAC) in its molecules that responsive for regulating and adopting its function for releasing proper results necessary for activating anti-inflammatory growth where the codons as Ile "ATT", Asp "GAT", Ser "TGA", Leu "CTT", Leu "CTC"

Gly "GGT") are necessary for strengthen such active pyrimidine kinases for building promoters within GC-beta, in B-arrestins and in Ang2-AT2 which can adopt the VEGF-A activity (and CTGF in adopting manner) for protecting heart activities and anti-inflammatory growth.

Also, the decreasing or inhibition in Ser amino acids synthesis will reflect Inhibition in pyrimidine synthesis, (regulated by OPA1 synthetase enzymes) associated with inhibition in both estrogen and in Carnitine palmitoyltransferase-1 (CPT1) synthesis that will lead to inhibition or decreasing in beta oxidation by OPA1 synthase, decreasing in GC-beta, and decreasing in both B-arrestins and Ang2-AT2 synthesis that will be associated with the accumulation of long fatty chains with decreasing in fatty acids oxidations "FAO" that will lead to increasing in K and Na binding molecules (due to decreasing in mineralocorticoid) that will lead to lipotoxicity and Atherosclerosis depending on the percentage of the decreasing in FAO and in the percentage of K accumulation.

The inhibition in pyrimidine kinases will lead to inhibition in beta oxidation and will cause inhibition in Carnitine palmitoyltransferase-1 (CPT1) and will lead to inhibition in FAO and associated with accumulation in long fatty chains (due to ATPase function on fat oxidations) and cholesterol in blood vessels.

Inhibition or deficiency in Tyrosine TAT and TAC codons (depending on the percentage of their Deficiency) will cause vasoconstriction and arrhythmogenecity due to accumulation in cholesterol and G-protein receptors (which promote increasing Ang1 AT1 that contain Tyr Codons TAA and TAG codons) [réf, Ashraf Marzouk El Tantawi proper Rac1 required for Ang2 - AT2....] that will lead to accumulation of long fatty chains and fatty Acyl-COA-gamma which have high binding affinity to K and Na with promising high stability within heart layers that will cause lipotoxicity and will block or reduce blood flow in blood vessels followed by reduction in both GCs-beta and in mineralocorticoid synthesis with decreasing in B-arrestins synthesis that will be associated with increasing in the precipitated long fatty chains and in glycoprotein bind with K and Na molecules that can cause Atherosclerosis.

Only due to inhibition in pyrimidine kinases with inhibition in estrogen, in GC-beta, in mineralocorticoid and B-arrestins will reflect accumulation in long fatty chains and cholesterol which will raise the binding affinity to k and Na salts with promising high stability which will elevate the risk of atherosclerotic cardiovascular events.

The deficiency or inhibition in pyrimidine kinases synthesis can reflect Inhibition in estrogen with increasing in cholesterol (due to inhibition in synthase effect on cholesterol for estrogen Biosynthesis) that will increase in blood and precipitated on blood vessels and will increase binding affinity to K and Na salts in heart layers and in blood vessels cause cytotoxicity.

That also increasing in cholesterol with decreasing in pyrimidine and decreasing in estrogen synthesis will reflect deficiency in the conversion of acyl-CoA to acylcarnitine which mediate GCs, in mineralocorticoid synthesis, and consequently in B-arrestins synthesis that will reflect reductions in Myocardial heart layer functions with increasing in long fatty chains, in cholesterol that can increase the binding affinity with k and Na in Myocardial and in Epicardium that will reflect their precipitations in heart and blood vessels that will cause reduction in blood flow and lipotoxicity.

The Interactions of fatty acids with the potassium channel KcsA has been detected with high affinity, that EPR studies with a spin-labeled analogue of stearic acid detected a high-affinity binding site for the fatty acid with strong immobilization [43].

That inhibition or decreasing in pyrimidine kinases (inhibition in estrogen), in GCs-beta and in mineralocorticoid will reflect accumulation in K and Na and precipitation of glycoprotein and long fatty chains (bind with K and Na) in blood vessels and in heart layers. Where, it has been detected Multiple Binding Sites for Fatty Acids on the Potassium Channel KcsA [44].

And the binding of K and Na salts to unsaturated fatty acids will inhibit the fatty Acyl-COA-beta production followed by inhibition in both GCs and B-arrestins synthesis. And it has been reported the Binding of unsaturated fatty acids to Na+,K+-ATPase leading to inhibition and inactivation [45].

Polyunsaturated fats has the roles of activating fatty Acyl-COA beta for promoting IFN-beta and glucocorticoid-beta necessary for B-arrestin synthesis:

Polyunsaturated fats include omega-3 and omega-6 fats that are essential fatty acids that human body needs for brain function, for increasing heart functions (in proper OPA1 function) and improving cell growth.

Polyunsaturated fats has the accelerating roles of activating fatty Acyl-COA beta and alpha promoted by tyrosine TAT and TAC kinases (regulated by OPA1 enzymes) which promote anti-inflammatory pathways (IFN-beta synthesis) and promote both glucocorticoids-beta and mineralocorticoid synthesis in Myocardial and epicardium heart layers where their functions include protection from K and Na binding molecules, and activating the adaptor B-arrestins for adopting ACE on the surface of the endothelial cells in Myocardial layer for adopting the Ang2-AT2 synthesis and then followed by VEGF-A synthesis for anti-inflammatory growth.

Acyl-COA is necessary for improving Long-chain acylcarnitine which can improve cells activities , where the role of carnitine palmitoyltransferase (CPT) 1 in FAO is critical Cpt-1β+/− for

develop cardiac lipotoxicity and exhibit increased pressure overload–induced cardiac hypertrophy.. ... [46].

And, the Overexpression of carnitine palmitoyltransferase-1 in skeletal muscle is sufficient to enhance fatty acid oxidation and improve high-fat diet-induced insulin resistance [47].

That, carnitine palmitoyltransferase-1 expression (basically regulated by pyrimidine kinases synthesis) are necessary for improving Ser palmitoyltransferase (SPT) enzyme.

Where, Serine palmitoyltransferase (SPT) (synthase dependent) is the first rate-limiting enzyme of sphingolipid synthesis, where the sphingolipids biosynthesis is the condensations of serine and palmitoyl CoA [48].

So in brief the pyrimidine synthesis for producing hydrophobic amino acids (as the Tyr, Leu, Ser, Cys ... etc) are so necessary for pyrimidine kinases functions, that Ser a.a. is necessary for Serine palmitoyltransferase (SPT) activated by carnitine palmitoyltransferase (CPT) 1 production which is critical for repairing cardiac lipotoxicity.

During stress, the carnitine begins to complete the cycle of fatty acids oxidation in order to steal the spotlight from the activity of ATPase (which responsible for producing energy through catabolic processes), then the Serine palmitoyltransferase (SPT) will produce from Acyl-COA-beta then will activate glucocorticoid-beta and beta-arrestin which will activate ACE for activating Ang2-AT2 productions from Ang1-AT1 which will protect the heart pulses and functions.

That, Myocardial carnitine palmitoyltransferase I (CPT1B) was already expressed before birth and that total CPT I expression transiently increased after birth in fetal and newborn lambs [49]. And, the Carnitine Palmitoyltransferase-1b Deficiency Aggravates Pressure Overload–Induced Cardiac Hypertrophy Caused by Lipotoxicity. Therefore, caution should be exercised in the clinical use of CPT1 inhibitors [50].

Carnitine Palmitoyltransferase-1b synthesis reflect the productions of acyl-CoA beta which reflect adopting to fatty acid oxidation to be enrolled in angiogenesis adopted activities, far from ATPase activities which can Aggravates Pressure Overload–Induced Cardiac Hypertrophy Caused by Lipotoxicity. The polyunsaturated fatty acids including Omiga 3 are having the roles of accelerating RORs pathways for accelerating the estrogen synthesis followed by Serine palmitoyltransferase productions followed by IFN-beta and glucocorticoid-beta which has the challenge roles for B-arrestins productions or Ang2-AT2 synthesis which improve and protect heart functions during stress and during pathogenic stress.

That, the Inhibition of Gene Expression of Carnitine Palmitoyltransferase Induce Acute Cardiotoxic in Rat Models [51]. Carnitine palmitoyltransferase-1 (CPT1) is a rate-limiting point and step of mitochondrial β-oxidation. It's clear that CPT1 has the strong roles of mediating the stimulation of both glucocorticoid-beta and mineralocorticoid synthesis in the endothelial Myocardial heart layer to prevent lipotoxicity and for protecting heart from both Na and K binding molecules followed by B-arrestins synthesis which adopt Ang2-AT2 synthesis which adjust heart pulses followed by running the full proper angiogenesis pathways.

Carnitine palmitoyltransferase I (CPT I) is the point step for catalyzing the conversion of acyl-CoA to acylcarnitine followed by Serine palmitoyltransferase productions (upon transferase effect), GC-beta, IFN-beta and mineralocorticoid synthesis through OPA1-synthase enzyme, that the deficiency in acylcarnitine synthesis will reflect the defects in mitochondrial beta oxidations by OPA1-synthase enzymes (that the deficiency in beta oxidations will reflect accumulation in long fatty chains and cholesterol), and can reflect deficiency in Ang2-AT2 synthesis lead to unadjusted heart contractions.

That it has been reported that the defect in Carnitine palmitoyltransferase I (CPT I can reflect improving in Myocardial Glycolysis [52]. The defect in Carnitine palmitoyltransferase I (CPT) reflect decreasing in Acyl-COA-beta then reflect decreasing in synthase function then consequently decreasing in pyrimidine synthesis and then reflect increasing in purine production and in S6K productions which produced upon purines kinases production due to Thr phosphorylation in mTOR pathway that will lead to activating ATPase that increase Glycolysis.

In brief Polyunsaturated fats has the necessary roles of activating fatty Acyl-COA beta and carnitine palmitoyltransferase (CPT) 1 production which improve fatty acids oxidations for promoting IFN-beta and glucocorticoid-beta for improving Myocardial layer functions and promote both mineralocorticoid (which prevent K and Na binding with lipids which cause lipotoxicity), and B-arrestins production (which regulated by both tyrosine TAT and TAC kinases and by estrogen synthesis).

Notice that estrogen synthesis depend on Ser phosphorylation in mTOR pathways for producing pyrimidine kinases necessary for Estrogen synthesis and for GC-beta and IFN-beta synthesis, while Thr phosphorylation are responsible for purines kinases production which promote S6K synthesis necessary for ATPase and GTPase productions [53].

Also, it's important to notice that serine phosphorylation pathways are necessary not only for Estrogen synthesis (where cholesterol is the substrate for Estrogen synthesis) but also necessary for myocardial heart layer functions through its involvement in Serine palmitoyltransferase (SPT) synthesis (synthase dependent enzyme) which needed for promoting fatty Acyl-COA-beta which needed for GC-beta and Mineralocorticoid improvements and B-arrestins productions in Myocardial heart layer which necessary for adopting and improving endothelial cells activities through adopting both of angiogenesis pathways through the Ang2-AT2 synthesis (from the excess of Ang1-AT1) and then adopting heart pulses in proper pumping for proper heart functions.

The Serine palmitoyltransferase (SPT) complements the proof of the value of the presence of Serine amino acids function in the activity of the heart layers, in addition to its presence is necessary in activating the cellular activities and angiogenesis necessary for improving anti-inflammatory growth and functions. The Ser TCC & TCG kinases are necessary for GTPase productions and for promoting cytosine methylation for charges transfers, While Thr "ACA & ACG" are responsible for promoting S6K and purines kinases production upon phosphorylation through mTOR pathway. That it has been reported that necessary for improving migration and improving cytosine methylation on DNA charges transport, where the charge transfer are necessary for improving lipotoxicity and migrating both K and Na-binding molecules far from heart through epicardium layer to kidney and skins pores [54].

Also it's important to note that Ser "TCC kinases", Tyr "TAC kinases ", and Cys "TGC kinases" are so necessary for activating

hydroxy methyl-Cytosine synthesis for activating both CMs and endothelial cells activities mediated by Ang2-AT2 productions and ACE regulations. That Hydroxymethyl-Cytosine activities (upon ACE 2nd domain functions) are necessary for activating ECs and modulating CMs functions throughout adjusting methylation and demethylation activities which create necessary signals that adjust Myocardial contractions and relaxations [55].

So, Tyr TAT and TAC kinases, Ser "TCC and AGC, Tyr "TAC, and Cys "TGC are necessary for improving GCs-beta synthesis and functions and consequently important in mineralocorticoid, in B-arrestins and in Ang2-AT2 molecules synthesis for proper improvement to their functions and for adopting heart pulses.

Increasing oxygen rich carbons will reduces myocardial functions by enhancing their binding with k /Na molecules with increasing in energy content in heart layers

Increasing oxygen rich carbons will inhibit or reduce OPA1 synthase and the production of estrogen from cholesterol which consequently will inhibit GCs and mineralocorticoid followed by reduction or inhibition in B-arrestins that will reduce Ang2-AT2 synthesis and will be result of reduction in running the adopted angiogenesis pathway that will reduce the protection to heart contractions and functions, and also will enhance the binding of both k and Na molecules to long fatty chains and cholesterol that reflects increasing in stability of K and Na binding toxic molecules that will damage endothelial activities.

That, it has been reported that theoretical calculations demonstrate that edge-N doping can enhance the local electronegativity of graphitic lattices to adsorb much more K+, and the oligomycin can be considered as high oxygen rich carbon that are an strong inhibitor to mitochondrial membrane function and can enhance the catabolic process and enhance the binding with Na and K to long fatty chains and to cholesterol with promising stability in their binding structure[56].

Where, It Has Been Reported That oxygen-rich carbon nanosheets is perfect atmosphere for enhancing k diffusion with high energy/ power density of 193 W h kg−1/22 324 W kg−1. Those high rich oxygen-carbons are sufficient to attract K with promising high stability by high density of diffusion for possessing high stability of K and Na binding toxic moleculer structures. Where repairing OPA1 synthase and Estrogen synthesis for B-arrestins will be the main key of processes to treat K and Na binding molecules [57].

The Oligomycin are an inhibitor to H+ATP synthase that consequently inhibit mitochondrial respirations and inhibit both GCs-beta and mineralocorticoid synthesis that consequently reduce or inhibit myocardial heart functions through inhibition in both Ang2-AT2 and VEGF-A which necessary for microvascular repair and functions. Where it has been reported that inhibiting mitochondrial oxidative phosphorylation disrupts endothelial control of vascular tone [58]. Also, Oligomycin inhibit mitochondrial OPA1 synthase and consequently inhibit several necessary dependent cellular pathways as BTK RORs, Rac1..... and B-arrestins productions.

The formation of oxygen rich carbons Molecules in myocardial heart layer is the main reasons for inhibiting fatty Acyl-COA-beta followed by inhibition in estrogen, Mineralocorticoid and B-arrestins that consequently will enhance the binding of both potassium "K" and Sodium "Na" to oxygen rich carbons and oligomycin that will produce stable toxicity in heart layers and in blood stream that will inhibit angiogenesis. That, Carboxyl Dominant Oxygen-Rich Carbons for Improved Sodium Ion Storage: Synergistic Enhancement of Adsorption and Intercalation Mechanisms [59].

That the repulsive force between carbons and carboxylic grows through electrostatic interactions will enhance Na- pre-adsorbed, and hence facilitate diffusion-controlled Na- insertion process for Binding in heart layers that will increase the affinity of binding to K with stability molecular structure which lead to inhibition to Endothelial cells functions.

The, increasing in oxygen rich carbon molecules (and in oligomycin) will reflect reduction in angiogenesis pathways and associated with toxicity in heart layers , in blood vessels that can reflect arthritis due to decreasing or inhibition in Rac1 which depends on mitochondrial OPA1 synthase and on pyrimidine kinases synthesis for improving its full functions pathways.

Where, it has been reported that The mitochondrial inhibitor oligomycin induces an inflammatory response in the rat joint [60].

The necessity of pyrimidine kinases for B-arrestins for adopting heart pulses for survival

The necessity of tyrosine TAT and TAC kinases in GC-beta and in B-arrestins synthesis indicate the necessity of B-arrestins for protecting and adopting heart pulses survival. That firstly tyrosine kinases regulate glucocorticoids functions , that the Tyrosine kinase inhibitors block the glucocorticoid stimulation of prostaglandin endoperoxide H synthase expression [61].

As the tyrosine TAT and TAC kinases are necessary for activating glucocorticoid-beta followed by B-arrestins synthesis (regulated by OPA1 synthase functions and Estrogen productions) as Tyr TAT and TAC are necessary for B-arrestins function which plays important role to stimulate ACE to promote Ang2-AT2 synthesis from Ang1-AT1 followed by for improving anti-inflammatory growth by VEGF-A synthesis for adopting microvascular repair and functions necessary for improving endothelial activities.

That It Has Been Reported That β-arrestin-2 alleviates rheumatoid arthritis injury [62]. That decreasing in pyrimidine TAT and TAC kinases will improve the decreasing in estrogen synthesis and in GCs-beta synthesis followed by decreasing in B-arrestins with increasing in purines TAA and TAG kinases (increasing in GPCRs) with accumulation in long fatty acids chains (due to decreasing in estrogen synthesis from cholesterol upon synthase effect) that will be precipitated in blood vessels, and in heart layers (cause increasing in CTGF which increases irregular growth in left vertical size), that will cause rheumatoid arthritis (decreasing in VEGF-A which promote bone growth). That also, VEGF is important for regulating osteoclasts in the remodeling stage [63].

And, the Deficiency of β-arrestin1 ameliorates collagen-induced arthritis with impaired TH17 cell differentiation [64]. So, inhibition in tyrosine TAT and TAC kinases will reduce or inhibit B-arrestins and Ang2-AT2 synthesis followed by inhibition in anti-inflammatory processes and in adopting heart pulses and heart functions followed by increasing in purines kinases which promote Syk production which activate the increasing in ATPase function with increasing in cholesterol accumulations (where ATPase contribute in the long fatty chains productions upon FAO)

that will lead to rheumatoid arthritis, or Atherosclerosis depending on the tissues which represent such deficiency in pyrimidine synthesis, that pyrimidine kinases has the function of building promoters in Ang2-AT2 molecules followed by VEGF-A which necessary for anti-inflammatory growth.

The inhibition or decreasing in tyrosine TAT and TAC kinases in heart myocardial layer will be the result of decreasing in GC-beta, mineralocorticoid, and B-arrestins, and Ang2-AT2 productions that will reflect increasing in long fatty chains and in cholesterol which reflect a high affinity of increasing in binding to K and Na molecules promising high stability with toxicity production with decreasing in heart pulses where has been improved previously their roles in increasing and adapting pulses throughout B-arrestins and Ang2-AT2 synthesis (and also the reduction in heart beats will help increasing in the precipitated cholesterol, K, Na, and glycoprotein), and will lead to increasing Ang1-AT1 activities and accumulation that will lead to increasing in CTGF that will lead to increasing in the unadopted unregulated growth (such growth in left vertical size too in some cases).

In brief, The production of GC-beta regulated by tyrosine TAT and TAC kinases are the main for B-arrestins productions (regulated by estrogen) which adopt and activate ACE for adopting Ang2-AT2.

Tyrosine kinases TAT and TAC necessary for heart constriction and for B-arrestins synthesis in Myocardial layer

Phosphorylation of both Tyr311 and Tyr565 is dependent on Src kinase and PLC (phospholipase C) activity in response to thrombin. Importantly, direct allosteric activation of PKCÎ´ with PMA also induced phosphorylation of Tyr311 and Tyr565, and this was dependent on the activity Src kinases [65].

Also TXA2 which promoted by pyrimidine kinases, Rac1, B-arrestins and by VEGF-A (which regulated by Ang2-AT2 promoted and adopted by B-arrestins) has been approved to cause constriction and develop coronary collateral vessels. That it has been reported that Thromboxane A2 and serotonin have been shown to cause constriction of well-developed coronary collateral vessels [66, 67]. Also, Protein Kinase Is required for Thromboxane- Induced Contractions in arteries. [68].

So, Previous studies indicated to me that Tyr (TAT and TAC) kinases are the necessary for B-arrestin (regulated by GCs and Estrogen) and for VEGF-A followed by TXA2 synthesis and for creating or inducing constriction in arteries and in Myocardial which result of creating or releasing signals changes from functions of pyrimidine kinases which involved in B-arrestins and in Ang2-AT2 heart layer that will cause constriction in heart layers (and in muscles) that migrate along blood vessels. Dynamic vertebral artery compression by lesions of the bone mass can appear with repeated beats until it creates strong repetitive pulses which basically originated from Tyr kinases phosphorylation process that will be adjusted by a full controlled system started by GCs-beta which promote B-arrestins synthesis that consequently will activate ACE to produce the Ang2-AT2 which adopt and protect heart beats which basically depend on the percentages of tyrosine TAT and TAC kinases in B-arrestins and in Ang2-AT2 molecules. The pyrimidine kinases has a wide regulation to cellular pathways that has the roles to activate endothelial cells through promoting the initiation of glucocorticoid-beta, and B-arrestins productions, that has the important roles to promote Rac1 productions too which has the roles to activate TXA2 synthesis and adopt microvascular functions which depends on pyrimidine kinases synthesis which contribute in the B-arrestins synthesis.

Where, The Endothelial Protein C Receptor (TAC kinases) initiates β-arrestin-2 biased signaling that results in the activation of Rac1 GTPase [69].

The active adaptor B-arrestin roles can reflect stimulating ACE for Ang2-AT2 synthesis from Ang1-AT1 for adopt both coagulation and fibrinolysis, and promote the active GPCR trafficking with arrestin-mediated signaling for Ang2-AT2 synthesis and running angiotensin signaling.

That B-Arrestins is adaptor active protein (upon tyrosine kinases, estrogen, and GCs regulation) that adopt Cardiac GPCRs kinases percentages and Signaling

The role of TAM receptors includes AXL receptor (which is tyrosine TAA and TAG kinase receptor) in heart functions

AXLs receptor tyrosine kinase is highly expressed in Myocardial and endocardium heart layers due to the availability of TAM receptors kinases in heart layers functions.

The TAM receptors are family of three receptor tyrosine kinases. includes an extracellular N-terminal region containing two immunoglobulin (Ig)-like domains, followed by two fibronectin type III (FNIII) domains, a hydrophobic domain which traverses the cell membrane, that TAM receptors have the ability to influence multiple aspects of cardiovascular pathology [70].

The presence of TAM three receptors will promote both pathways

_firstly the Ang1-AT1 synthesis,
_secondly the GCs-beta and B-arrestins synthesis which will activate ACE for Ang2-AT2 synthesis followed by VEGF-A productions for adopting anti-inflammatory growth that recover the cells death.

The decreasing in TAM hydrophobic domain which traverses the cell membrane (FNIII), will reflect decreasing in GCs-beta and in B-arrestins synthesis followed by decreasing in Ang2-AT2 synthesis,, followed by increasing in AXLs receptors which activate Ang1-AT1 and will activate CTGF production that will increase irregular growth.

Peripheral sAXL receptors are formed from tyrosine TAA and TAG receptors kinases that are carrying the role of progression myocardial functions through involvement in the TAM receptors kinases which contains the three tyrosine receptor kinases Tyro3, MerTK (pyrimidine kinases), and the AXL receptors kinases, where MerTK are the domains that contain hydrophobic amino acids that responsible for activating Acyl-COA-beta synthesis which promote GCs-beta (upon beta oxydation) followed by B-arrestins synthesis and then followed by Ang2-AT2 synthesis upon ACE functions, then followed by activating anti-inflammatory growth by VEGF-A productions.

The decreasing MerTK (pyrimidine TAT and TAC kinases domains) will reflect decreasing or inhibition in both estrogen and B-arrestins synthesis followed by decreasing in Ang2-AT2 synthesis and in VEGF-A synthesis and functions. Also, The decreasing and MerTK (pyrimidine TAT and TAC kinases) will reflect increasing in the glycopeptides accumulation and in ATPase activities due to increasing in TYRO3 and AXL receptors activities.

The increasing in GPCRs accumulation eil' activate CTGF activity for irregular growth (due to absence or decreasing of VEGF-A synthesis) that will lead to atrial fibrillation, and in cause of binding the GPCRs with k and Na will lead to increasing in cardiac toxicity and heart failure.

Heart failure are associated with increased AXL receptor membrane level that as AXL is one of the three TAM receptors, that as MerTK domain inhibited (pyrimidine TAT and TAC kinases) followed by inhibition in Tyro3as domain as the accumulations of AXL Tyr receptor occured which associated with heart failure patients.

That the tyrosine kinases receptors (MerTK domains) are necessary for promoting GC-beta, Mineralocorticoid, B-arrestins, which necessary for adopt endothelial myocardial functions, through activating ACE for Ang2-AT2 synthesis from Ang1-AT1 followed by activating anti-inflammatory growth through VEGF-A synthesis.

The, inhibition in pyrimidine "tyrosine TAT and TAC" kinases will give the priority for increasing in the accumulated AXL tyrosine (TAA and TAG kinases) receptor and in TYRO3 domain(which activate ATPase activity) with increasing in glycopeptides and in the accumulated long fatty chains which will cause lipotoxicity, but if the accumulated fatty chains and glycoprotein bind with k and Na will cause Hyperkalemia and precipitation in hart layers and on blood vessels.

The inhibition in Src pyrimidine kinases will increase the glycoprotein level and increase AXL tyrosine receptor (which is Tyr TAA and TAG receptors) that can increase the circulating endothelin-1 levels through increasing in building Ang1-AT1 and increasing in AXLs receptors levels in blood.

Where it has been reported that, Hypertension induced by the tyrosine kinase inhibitor sunitinib is associated with increased circulating endothelin-1 levels [71].

The inhibition in MerTK receptor domain in TAM receptors will lead to the increasing in AXLs (TAA and TAG receptors) level which will promote the increasing in ATPase functions and lead to increasing in glucose metabolism with increasing in AXL receptor which associated with heart failure.

Where, it has been reported that, AXL receptor tyrosine kinase is increased in patients with heart failure [72]. Also, Macrophage AXL receptor tyrosine kinase inflames the heart after reperfused myocardial infarction [73].

While MerTK are the main domain in TAM receptor kinases that activate anti-inflammatory growth (which mediated by Ang2-AT2 productions) to protect from Rheumatoid Arthritis [74].

And, Axl expression is increased in early stages of left ventricular remodeling [75].

So, I can conclude that : the TAM receptors kinases functions has the roles for promoting and activating myocardial full functions through activating Acyl-COA beta production (regulated by hydrophobic receptor domains) which promote GCs-beta upon beta oxidation (regulated beta oxidation by synthase and by Carnitine Palmitoyl Transferase) followed by B-arrestins synthesis (regulated by GCs-beta and Estrogen) which stimulate ACE functions for Ang2-AT2 synthesis followed by VEGF-A synthesis which activate the anti-inflammatory growth, then followed by the free AXL receptor from the TAM receptors kinases (due to the Ang2-AT2 synthesis in Myocardial layer) will be released freely to be migrated to endocardial layer to blood stream.

The inhibition in the TAM and MerTK receptors will lead to inhibition in Myocardial functions that will lead to toxicity in heart layers and can cause hypertrophy (LVH) followed by heart failure with the association of the AXL receptors domains (which basically activate Ang1-AT1 and ATPase functions). And, the availability of B-arrestins synthesis in Myocardial layer will adopt the increasing in AXLs receptors domain levels through promoting Ang2-AT2 synthesis from Ang1-AT1 followed by activating VEGF-A productions for anti-inflammatory growth.

The Phosphatidyl-serine Can bind to TAM receptors kinases upon beta oxidation Followed by Serine palmitoyltransferase for running ceramide Biosynthesis processes which can activate Acyl-COA-beta followed by GCs-beta synthesis in Myocardial heart layer, that the Inhibition of Serine Palmitoyl Transferase will Increases Glycolysis due to the increasing in AXL receptor kinase activities which increases ATPase activities. The Serine amino acids as hydrophobic amino acids are necessary for Serine palmitoyltransferase (SPT) (Ser phosphorylation required for promoting estrogen synthesis upon beat oxidations by synthase on cholesterol) are necessary for promoting Acyl-COAbeta (upon beta oxydation) which will promote angiogenesis pathways by Ang2-AT2 synthesis which will elease active signals that will adopt heart pulses then followed by activating anti-inflammatory growth through VEGF-A productions which necessary for improving ischemic injury. That, Serine palmitoyltransferase activity increased along with development on P8, P10, P14 and P21.

And, the Inhibition of Serine Palmitoyl Transferase I Reduces Cardiac Ceramide Levels and Increases Glycolysis Rates. That, inhibition of de novo ceramide synthesis, that SPT I inhibition will reflect Inhibition in Carnitine Palmitoyl Transferase functions followed by inhibition in beta oxidations that will lead to increasing in purines kinases which will increase the ATPase activity that will increases cardiac glucose utilization. But it looks to me that inhibition in serine palmitoyltransferase will reflect Inhibition in pyrimidine kinases and consequently inhibition in Carnitine Palmitoyl Transferase functions followed by inhibition in beta oxidation then consequently inhibition in Acyl-COA-beta followed by inhibition in B-arrestins and in Ang2-AT2 synthesis which will reflect Inhibition in VEGF-A activities followed by inhibition in the anti-inflammatory growth.

Conclusion

The development of Cardiomyocytes cells depend on endothelial cells functions which controlled by B-arrestins which adopt ACE that located on the surface of endothelial cells for adopting Ang2-AT2 synthesis for adopting heart activities and constrictions followed by activating VEGF-A necessary for anti-inflammatory growth.

pyrimidine "TAT and TAC" kinases and peroxiredoxin 1 (PRDX 1) are necessary for activating ACE to adopt Ang2-AT2 productions and activating anti-inflammatory growth via VEGF-A productions. So PRDX1 play basics roles in protecting and adopting heart pulses in proper conditions. Vascular endothelial growth factor (VEGF) (adopted by Ang2-AT2 synthesis and functions) has its strong basis roles for activating and protecting human microvascular endothelial cells (HMVECs) activities and functions which mainly regulated and protected by peroxiredoxin 1 which protect both Estrogen (and B-arrestins too) followed by Ang2-AT2 synthesis for promoting anti-inflammatory growth via VEGF-A productions.

In this study, I clarify the functions of each of the myocardial layers, and the latter depends B-arrestins and Ang2-AT2 which are having most important of protection to heart functions and having the function of creation and adopting the heart constriction.

I clarified The mechanisms and Pathways that are important and can take place done within the myocardial for improving epicardial cells function for protecting heart function through beta-arrestin and Ang2-AT2 synthesis followed by VEGF-A synthesis which promote anti-inflammatory growth. Also it has been discussed and noted the fibrolysis mechanism and their role that help to protect the heart vitality and activities and protect the blood flow, and the importance of the presence of Omega 3 in the activation of the heart and the activation of the formation of Serine palmitoyltransferase (SPT), which accelerate the formation of both IFN-beta, GCs-beta and B-arrestins which are important for improving heart functions through activity of Ang2-AT2 synthesis which protect heart functions and adopt heart pulses.

also it has been declared in this study the danger of the formation of oxygen rich carbon molecules and the long fatty chains which have high affinity to bind with both potassium and sodium lead to the formation of toxicity and lipotoxicity in heart layers and in blood vessels.

Also, I would like to note that we can considered that glucocorticoids-beta, Mineralocorticoid, and B-arrestins can be regulated and recovered by Rac1 function (which regulated by pyrimidine TAT and TAC kinases too), and also Ang2-AT2 and its regulated and adopted VEGF-A synthesis are Regulated by Rac1, by ROR beta synthesis pathway, by Serine palmitoyltransferase (SPT), and by both GCs-beta and B-arrestins synthesis and functions where are necessary for protecting heart activities, and vitality of functions.

Also, I declared that the Porposes of this study is to understand clearly each of heart layer functions and the reasons of causing heart diseases such as lipotoxicity, increasing in left vertical size, and, Hyperkalemia, that we can easily treat each of heart disease directly by injection with specified needed active subunits and effective genes such as Beta-Aristin, and minerallomorticoids (rich in proper pyrimidine TAT and TAC kinases and rich in necessary hydroponic acids such as Tyr, Ser, Leu, Île) directly to the layer intended for treatment in the heart muscle to restore the heart function and adopted pulses, to treat stroke (starting by heart treatment), or to analyze high stable K and Na binding molecules, and to reactivate of the heart valves vitality and restore the activity of aorta. Improving in treating heart diseases throughout direct injection to one or two specified heart layer will help to move away from the dangers of open-heart surgery, then will accelerate the development of heart activities with safety and protections to the patients and to their heart vitality with decreasing in the risk of danger and damage in heart muscles and capillaries. Notice direct injection with B-arristin (the adopter protein rich of pyrimidine kinases necessary for building their promoters TAT and TAC), and Ang2-AT2 to heart layers are having enough safety and protection necessary in critical times.

Conflict of Interest

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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