Advances in Clinical and Medical Research

Genesis-ACMR-3 (3)-35
Volume 3 | Issue 3
Open Access
ISSN: 2583-2778

Rac1 AT1 required for Ang2-AT2 Activities for Cardiomyocytes and ECs where Tyr TAT and TAC Kinases required for Preventing Glycoprotein Storage and Glycogen Accumulation

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Citation: El Tantawi AM. (2022) Rac1 AT1 required for Ang2-AT2 Activities for Cardiomyocytes and ECs where Tyr TAT and TAC Kinases required for Preventing Glycoprotein Storage and Glycogen Accumulation. Adv Clin Med Res. 3 (3):1-29.

Received: July 07, 2022 | **Published**: July 30, 2022

Abstract

Active Rac1 are so imp for improving cytoskeletal systems and for improving anti-inflammatory processes by activating Plcγ2, IFN-beta and glucocorticoid-beta (which necessary for B arrestin synthesis which necessary for activating endothelial cells function through activating ACE functions). Tyrosine kinases function (contain TAT and TAC codons) are so necessary for activating Ang2-AT2 productions for adjusting heart contractions and preventing collagen, glycoproteins, and cholesterol accumulations. Angiotensin II type 2 receptors (Ang2 bind to AT2 receptors) are produced from Ang1-AT1 by ACE regulated functions in Tyr kinases-dependent (which contain TAT and TAC codons), where Tyr codons are playing imp roles in AT1 and AT2 activities play important roles in protecting heart and blood vessels from accumulated cholesterol and glycopeptides and from accumulated glycogen. The deficiency in synthetase and in Proline (which promote amino acids synthesis regulated by aminotransferase activities) can cause accumulation of purines nucleotides which Represents or leads to glutamate accumulation and lead to accumulation of glycogen synthase where glycogen accumulation due to Tyrosine Codons TAA and TAG accumulation in the form of glycopeptides and glycoprotein with decreasing in imp

DOI: https://doi.org/10.52793/ACMR.2022.3 (3)-35

Tyrosine Codons TAT TAC (pyrimidine kinases) which play important roles in building dynamic promoters in Ang2-AT2 active molecules. The deficiency in pyrimidine synthesis due to deficiency in synthetase functions will cause deficiency in pyrimidine kinases and mutations in thymine kinases and in cytosine pyrimidine kinases. Also deficiency in pyrimidine kinases will lead to increasing in Ang1-AT1 activities " that will promote maturation including allergic inflammations and tumors mediated by mutated CTGF productions and will associated with decreasing in signals productions (necessary for adjusting heart beats. Also deficiency in Estrogen productions (due to decreasing in pyrimidine kinases with increasing in purines kinases) that will lead to cholesterol accumulation and decreasing in B-arrestin that will not activate ACE for reactivate endothelial cells function.

Abstract

BTK and Ang1 AT1 are so necessary for IgM and IgG3 synthesis in blood serum that can be considered as so necessary for anti-inflammatory improvement, but in case of the absence of Tyr Codons TAT & TAC (kinases) the BTK will be critical for increasing the accumulated collagen (accumulated glycoprotein) in arteries which are critical for the tumor synthesis.

Glycogen storage disease (GSD) and glycoprotein storage disease (GSD) are started by sever deficiency in Tyrosine TAT and TAC pyrimidine kinases (which reflect deficiency in Ang2-AT2 productions) that will lead to accumulated glycogen (increasing in Ang1 AT1 activity and glycoprotein accumulations), where, Ang2-AT2 productions are necessary for binding to the stored glycogen with metalloproteinase dependent for platelets activation mediated by releasing nitric oxide. 5-hmC are considered as the enhancers and the key regulators in heart developments, contractions, and blood vessels protections, where 5-hmC regulated by pyrimidine kinases and is so necessary for adjusting muscles contractions through methylation and demethylation processes.

Inhibition in Ang2-AT2 functions will lead to Endothelin A (ETA) receptor blockade and will lead to increasing in Ang1-AT1 activity and can cause glycoprotein storage, glycogen accumulation in Blood vessels (depend on the quantity and type of Ang2-AT2 inhibition) and will promotes adverse ventricular (LV) dilatation.

Angiotensin I-Converting Enzyme "ACE" consists of two active domains and is found on the surface of endothelial and epithelial cells throughout the body [Soubrier et al (1998)], that as ACE consists of two catalytic domains located on the surface of endothelial cells as it looks to me that one of ACE domain "1st domain" contains Tyr TAA and TAG which can reactivate Ang1 synthesis, while the other 2nd ACE domain contains the necessary Tyr Codons TAT and TAC which necessary for reactivating Ang2 AT2 from Ang1, That ACE "2nd domain" acts on AT1 for AT2 synthesis but it's main sits for acting are the phenylalanine and Tyrosine, where In the deficiency in 2nd ACE domaine will be the result of Deficiency in AT2 and then reductions in migrating Molecules and consequently will lead to accumulation in glycogen in arteries and decreasing in platelets activation then in long term of decreasing in ACE 2nd domain with increasing in maturation by Ang1 will be the result of increasing in left vertical size and

DOI: https://doi.org/10.52793/ACMR.2022.3 (3)-35

then dropping in blood pressure. Note that increasing in adverse ventricular (LV) dilatation due to inhibition or deficiency in Ang2-AT2 synthesis (deficiency in pyrimidine kinases) will lead to increasing in Myocardial relaxation time that will be main reason in hypotension which due to increasing in ventricular volume leads to an increase in the diastole of the heart due to increasing maturation and proliferation by Ang1 AT1 that lead to Vascular blockage and vasocon striction and arrhythmogenecity that (depend on the percentage and type of Ang2-AT2 inhibition.

Inhibition in pyrimidine kinases will lead to inhibition in Ang2-AT2 that can lead to increasing in glycoprotein storage in blood vessels (and glycogen accumulation) and can lead to increasing in left vertical size and sudden cardiac arrest.

Introduction

Angiotensin 1 is the precursor for angiotensin 2, where the main function of angiotensin 2 is causing constriction to blood vessels in order to raise and giving adjust blood pressure. Angiopoietin-1 and Angiopoietin-2 are glycoprotein that mainly regulated by by purines and pyrimidine kinases which produced from Ser/Thr--mTOR phosphorylation pathway which are P-Ser/Thr-Thymine Kinases ("pyrimidine kinases " promote Angiopoietin-1) and by Ser/Thr-Cytosine-kinases ("Pyrimidine kinases" promote Angiopoietin-2), P-Ser /Thr adenosine kinases (which considered as purine kinases that promote Ang1 AT1 productions), and P-Ser /Thr -guanine kinases (which considered as purines kinases for Ang1-AT1 synthesis), where Ang-1 is main source for growth factors CTGF productions, while Angiotensin II is known to induce Angiopoietin-2 and vascular endothelial growth factor. Where, Active Rac1 improves pathologic Vascular Endothelial Growth Factor (VEGF) neovessel architecture and reduces vascular leak: mechanistic that the active Rac1 which is necessary for activating similarities with the utangiopoietin-1 [1]. Ang2 administration led to the production of catabolic proteases and a decrease the aggrecan molecules and collagen II levels, and the Ang2 expression has been correlated with the speed of bone healing but in leukemia patients they have higher Ang2 levels had longer event-free survival rates [2,3].

That, Ang2 functions are the binding to aggregated glycoprotein and collagen through metalloproteinase dependent for releasing Nitric Oxide as a result of Platelet activations and reback for recover Ang1 activity (regulated by active ACE domains), that Ang2-AT2 can be considered as a typical tRNA that activate catabolic process through methylation and demethylation followed by increasing in the migrations for adjusting heart contraction and protect blood vessels from accumulated molecules, that its clear that Ang 2 is connected to bones synthesis and their speed of healing indicates that Ang2-AT2 is basically connected to and with the active Rac1 (rich Proline) functions pathways. But note that leukaemia disease due to sever deficiency in pyrimidine synthesis and deficiency in Rac1 proper structure (that deficiency in Proline in Rac1 will lead to decreasing in amino acids synthesis), and deficiency in necessary Tyrosine "Codons" kinases "Tyr TAT and TAC as pyrimidine kinases" will be result of inhibition in building dynamic promoters in Ang2-AT2, and in necessary genes including PLCγ2,IFN-beta, that the absence of pyrimidine kinases synthesis and Availability of only purines or more purines than normal percentage of pyrimidine will cause mutation in necessary genes including Ang2-AT2, Plcγ2

DOI: https://doi.org/10.52793/ACMR.2022.3 (3)-35

and IFN-beta that will be the result of pathogenic symptoms and appearance of Ang2 levels with longer event-free survival rates.

And it's clear to me that Ang2 AT2 is a "tRNA" that speed up its own catabolic processes methylation and demethylation (through producing 5-hmC) for increasing molecules migration and create necessary pulses for adjusting heart contractions and blood pressure upon Tyr Codons kinases phosphorylation processes (Pyrimidine kinases), and is carrying the roles of recover Ang1-AT1 activities (regulated by the two ACE active domains) which can stimulate Rac1 activities and can recover heparin function and vice versa that will discuss it later. Proper Ang2-AT2 has proper activities depending on proper tyrosine kinase receptors functions, where Ang2-AT2 acts as an antagonistic factor (anticoagulant) and activates hydroxy methyl-Cytosine which increases methylation and demethylation that adjust heart contractions. where Ang2-AT2 basically regulated by the protein-Ser/Thr-Thymine-kinases (Pyrimidine kinases) and protein-Ser/Thr-Cytosine-kinases (pyrimidine kinases) synthesis which depend on the availability of Serine amino acids in the mTOR Ser /Thr phosphorylation pathway, where those pyrimidine kinases regulate and activate BTK pathways and promote both CMs and ECs activities.

The Endothelial Cells Activated by C-protein "Ang2 AT2"

(Pyrimidine kinases) productions from the Ang1 that inhibits (or adjust) coagulation together with its cofactor protein S, that C-protein has the characterization of active tRNA that depends on cytosine kinases availability which stimulate the processes of methylation and demethylation which stimulate and adjust heart contractions and perform migrations to active subunits and molecules. The Rac1 has the activities of recover Ang1 which has the role of speeding bones healing through reactivating PLCγ2 synthesis and then TXA2 synthesis. That, Ang1-AT1 has the function of adjusting vascular protections through promoting Ang2-AT2 production upon ACE functions which necessary for cells survival for long term and prevent endothelial death through the ability of Ang1-AT1 for recover CMs which followed by Ang2-AT2 production upon ACE which found on the surface of epithelial cells adjacent to CMs for activating both Ang1-AT1 and Ang2-AT2 synthesis for protecting both cells (regulated by necessary normal Tyr Codons kinases) for adjusting heart contractions and recover Ang1-AT1 through feedback that can activated in kidney by renin function.

The increasing in Tyr purines kinases will activate Ang1 and its receptor that will promote maturation and proliferation and activate Ang2 and its receptors AT2 productions upon ACE functions and specific Tyr kinases activities (which carry the necessary Tyrosine codons "TAT and TAC" which activate Ang2-AT2 productions for controlling Ang1 activities), that if tyrosine pyrimidine kinases (contain TAT and TAC) the Ang2-AT2 will be decreased or mutated that will be the basic for myocardial infarction (MI)) that will give priority to Ang1 AT1 proliferative activity to work freely without control that can lead to increasing in left vertical size due to decreasing in Ang2 AT2 (and decreasing in adjusting heart contractions) that in long term will Lead to hypotensive and then heart failure. That, Endothelin A (ETA) receptor blockade started early after myocardial infarction (MI) promotes adverse left ventricular (LV) dilatation [4]. Also it has been considered that Angiotensin II enhances endothelin-1-induced vasoconstriction through upregulating endothelin type A receptor [5].

The mutated Angiotensin II which lack Tyrosine TAT and TAC codons has the activity of enhancing endothelin-1-induced vasoconstriction through decreasing its control to Ang1 AT1 proliferative activities and will lead to glycoprotein and glycogen accumulation in blood vessels with decreasing in platelets activation (which regulated by Ang2 AT2 binding to glycogen in metalloproteinase dependent). The inhibition in Ang2-AT2 functions means Endothelin A (ETA) receptor blockade that will lead to glycoprotein storage and glycogen accumulation in Blood vessels (depend on the quantity and type of Ang2-AT2 inhibition) that can promotes adverse ventricular (LV) dilatation (depends on the percentage and the type of tissues that contain the Endothelin A (ETA) receptor blockade). But, abnormal Angiotensin II which Deprived of the availability of necessary Tyrosine Codons TAT and TAC kinases will enhances endothelin-1-induced vasoconstriction through enhancing the Ang1-AT1 activities that will lead to glycoprotein perception in blood vessels and increase CMs activities with failing or decreasing in ECs functions.

The quantity of accumulated Collagen and glycoprotein is depending on the percentage of Deficiency in Tyrosine TAT and TAC codons that can be the result of vasoconstriction and arrhythmogenecity due to increasing in Ang1 AT1 which contain Tyr Codons TAA and TAG which upon phosphorylation will activate AT1 receptors (purines kinases) that can lead to myocardial infarction (MI) which promote left ventricular (LV) dilatation, and may can cardiac fibrosis too. Where, the excessive deposition of collagen, leading to cardiac fibrosis, is a major determinant of cardiac dysfunction and arrhythmogenecity associated with sudden death [6].

The necessicity of Rac1 in activating CMs and endothelial cells started by Tyr and hydrophobic acids synthesis that promote Tyr kinases cycles. While Rac1 contribute in the endothelial junctions, it becomes part of a barrier-disturbing mechanism as activator of reactive oxygen species generating NADPH oxidase [7]. Rac1 contribute in the endothelial junctions, through firstly produce PLCγ1, IFN-Gamma, PLCγ2, and IFN-beta respectively that will be the result of disturbing intracellular processes where Rac1 function depends mainly on Proline which regulate hydrophobic amino acids synthesis including Tyr amino acids which is necessary for producing Tyr kinases regulated by BTK activities (with necessary Tyr Codons) for regulating both Ang1 AT1 and Ang2-AT2 synthesis.

The normal activities of Rac1 disturbs the plasma or interstitium flud activities for begins to form its basic units in the orders that begins with PLCγ1 and (IFN-Gamma) and ends with the formation of TLR4 and PLC-alpha (for avoid any errors form other genes or enzymes activities). Rac1 disturb media in vivo In response of the signals coming from cells for producing firstly PLCγ1 acting on biological molecules followed by pyrimidine synthesis (regulated by synthetase) and hydrophobic amino acids synthesis (regulated by Proline and aminotransferase) for preparing necessary amino acids basically including Tyr Codons which necessary for re-activating BTK and for Ang1 production in liver and for building Plcγ2 subunits which stimulate the activity of ECs throughout Ang2 and AT2 synthesis followed by TXA2 synthesis and platelets activations which regulated by activity of Ang2-AT2 for producing glycogen receptors activated by Tyr kinases & BTK for platelets activations, notice accumulation of glycogen on arteries reflect deficiency in Tyr phosphorylation and deficiency or inhibition in platelets activation (that

DOI: https://doi.org/10.52793/ACMR.2022.3 (3)-35

will be clarified in this study later).

proper active Rac1 rich Proline are so imp for running and adjusting several of cellular activities (but not part of disturbing internal mechanism) including activating endothelial junctions and activating CMs necessary functions mediated by PLCγ2 and IFN-beta synthesis for TXA2 synthesis and for the long cells survival that will be mediated by adjusting and preventing hyperglycemia. That, Rac1 are so necessary for cardiomyocyte "CMs" apoptosis during hyperglycemia [8]. The necessity of Rac1 (which mainly regulated by Protein -Ser/Thr-Thymine-kinases synthesis form mTOR Ser /Thr phosphorylation pathway) is addusting hyperglycemia through stimulating synthetase functions for using extra purines for pyrimidine synthesis that will be followed by amino acids synthesis regulated by Proline and aminotransferase.

For Activating Tyr (Necessary Codons) Kinases Productions

For activating Ang1 AT1 and Ang2-AT2 production for adjusting heart contractions that finally hyperglycemia has been adjusted mediated by Gp-GTP subunits synthesis. Also, glycogen accumulation in smooth muscle cells of intramyocardial arteries associated with smooth muscle hyperplasia and profoundly thickened vascular walls. [9] indicating that deficiency in Rac1 rich Proline will be the result of accumulation of purines in the form of glycoproteins and glycogen (associated with Deficiency in amino acids synthesis) and decreasing Tyr kinases and reduction in the normal Ang2-AT2 activities that will reduce heart contractions and efficiency. The proper active Rac1 is carrying important regulation for cellular activities that can adjust and Prevent excessive relaxation of the heart muscle, where the accumulated glycopeptides and glycogen can reflect a dropping in blood pressure and decreasing in heart functions, and can conclude failing in adjusting hyperglycemia which mediated by Gp GTP subunits productions for reactivating both Cardiomyocytes (CMs) and endothelial cells - (ECs) mediated by Tyr kinases activities for producing Ang1 AT1 which activate Ang2-AT2 productions which adjust heart contractions and functions. The proper Rac1 rich of Proline are so necessary for promoting amino acids synthesis which necessary for regulating PLCγ2, IFN-beta, and both Ang1 AT1 and Ang2-AT2 synthesis mediated by Tyr kinases functions and Gp GTP subunits synthesis (Rho family) which promote ECs which adjust heart beats and hyperglycemia and preventing glycogen accumulations, followed by cells growth and proliferation.

Rac1 is the main necessary active biological molecules that can considered as the controller Rac1 genes (CRG) that are necessary for regulating Gp GTP subunits synthesis which activate Cardiomyocytes "CMs" activities regulated by Tyr kinases for promoting endothelial cells "ECs" activities through increasing the Endothelial junction and then through improvement the VEGF-driven angiogenesis, and are so necessary for neovascularization in vivo (mediated by PLCγ2 and IFN-beta productions).

Rac1 are so necessary for regulating IFN-beta and PLCγ2 which necessary for TXA2 synthesis and platelet activation where, fibrin imp for activating CMs and endothelial cells

That PLCγ2 has necessary functions for regulating TXA2 and reactivating platelets [10]. Receptor-mediated platelet activation requires phospholipase C (PLC) activity to elevate intracellular calcium and

induce actin cytoskeleton reorganization [11]. The Rac1 required for adjusting cellular activities mediated by Rho family (Gp GTP subunits) productions through the activating of the small GTPase Rac subunits which is essential for gene expression and for providing spatial information for shear stress-induced cell alignment [12]. The production of the three Gp GTP subunits regulated by proper " Rac1" molecules synthesis are so imp for controlling cells alignment and endothelial junction mediated by a variety of signal transduction processes including G-actin activities (which regulated by Gp GTP subunits synthesis). It is so imp to note that the availability of proper Rac1 rich Proline synthesis are so necessary for creating and adjusting the signals transmissions mediated by Gp GTP subunits productions which can reflect the proper improvement to endothelial cells activities, and reflect the improving of heart cells efficiency and are playing imp roles in shearing stress-induced cell alignment. Where, Proline-rich Region of Non-Muscle Myosin Light Chain Kinase Modulates Kinase Activity and Endothelial Cytoskeletal Dynamics [13], that previous study indicate necessity of Proline in regulating kinases activities through its roles in amino acids synthesis including Tyr synthesis which activate Tyr kinases upon phosphorylation in BTK pathways.

So the activation of the proper Rac1 in Non-Muscle Myosin Light Chain Kinase can activate both cardiomyocyte and the endothelial cells "ECs" functions through modulating kinase functions which mediate endothelial functions which are responsible for shearing stress-induced cell alignment that we can confirm the presence of Proline in Rac1 activities is playing imp roles in activating and adjusting heart functions through Cardiomyocytes "CMs" and endothelial cells mediated by the productions of Gp-GTP subunits (which can promote the Adrenergic receptors which belong to the superfamily of G protein-coupled receptors that plays imp roles in vasodilation through activating CMs and ECs mediated by PLCs and IFNs for anti-inflammatory processes and anti-inflammatory growth. But it's imp to note that L-leucine is playing imp role through mediating cardiovascular in CMs [14].

Leucine Mediate Cms Activation through Stimulating

Glutamine 6-phosphate aminotransferase synthesis where glutamine:6-phosphate aminotransferase (GFAT) is necessary for. Proline synthesis and amino acids synthesis (which regulated by Proline) and consequently the GFAT is the main activator for Tyr kinases synthesis. Note that Leu promote glutamine :6-phosphate aminotransferase synthesis by translation process as seen in this figure:

"GAA" Glu <¬>"CTT" Leu

"GAG" Glu <¬>"CTC" Leu

But need to realize that Leu is a main activator for hydroxy methyl-Cytosine which activate Ang2-AT2 and act as t-RNA for adjusting ECs functions, heart contraction and protect the high efficiency of blood vessels and adjust CMs activities through ACE 1st domain functions (which Ang1 AT1 productions) and renin functions. Kinase (ERK) pathway and B-arrestin regulate the excess of β-adrenergic receptors through preventing glycoprotein and glycogen accumulation. β-arrestins have been shown to act as physiologically relevant signaling molecules for many G protein-coupled receptors (GPCRs) across various cell and tissue systems [15], β-AR stimulation is a primary control point for modulation of heart rate and myocardial contractility. [16]. β-arrestins were originally described as proteins that desensitize G protein-coupled receptors, but they can also mediate receptor internalization and G protein-

independent signaling [17]. β-arrestins not only desensitize GPCR transduction pathways but also activate a second signaling pathway downstream of the GPCR transduction pathways. Further, β-arrestins can form complexes with several signaling [18]. β-Arrestin–Mediated Angiotensin II Type 1 Receptor Activation Promotes Pulmonary Vascular Remodeling in Pulmonary Hypertension [19]. β-arrestin contains Tyr Codons kinases (TAT and TAC required for building the necessary promoter which activate and control both Ang1 AT1 and Ang2-AT2 synthesis) that doesn't affect on activating G-proreins growth but can adjust the excess of purines kinases (where need purines kinases for activating Ang1 AT1 receptor glycoprotein for maturation), where β-arrestin can activate the second pathways for activating Ang2-AT2 synthesis by activating more of Pyrimidine kinases which Promotes Pulmonary Vascular Remodeling in Pulmonary Hypertension and re adjust heart contractions. Where deficiency or inhibition in β-arrestin will reflect deficiency in both 1st and 2nd pathways and can reflect deficiency in pyrimidine synthesis and may deficiency in specific steps for producing purines kinases which basically depend on S6K productions. Despite the importance of β-arrestin, there is an expected possibility that the decreasing in its percentage may reflect deficiency or inhibition in both pyrimidine and in S6K productions which produced from the Ser /Thr mTOR phosphorylation pathway that may can reflect reductions in ROR gamma and beta pathway. That Adrenalin stimulation can increase the glucose uptake in a limit in brown adipose tissue, [20]. Adrenalin stimulation will increase the glucose uptake through increasing in S6K, ATP, and GTP activities (Figure1-4).

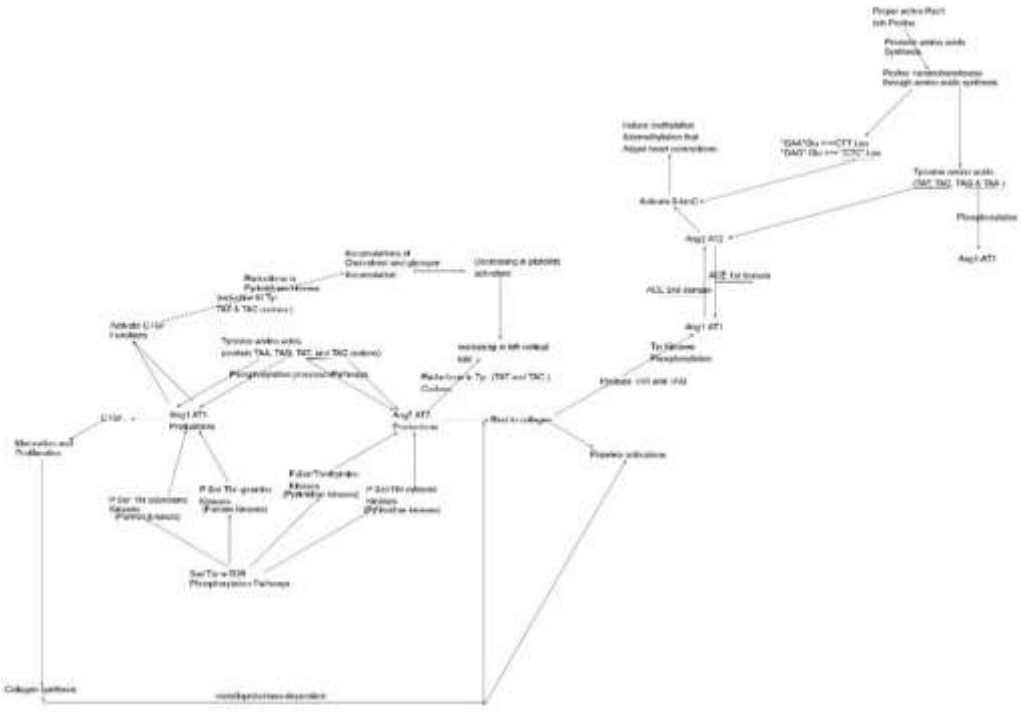

Figure 1: Pathways of Ang 1, AT1 synthesis and Pathways of Ang2- AT2 synthesis from Tyr amino acids and from Ser/Thr mTOR Phosporylation Pathyways.

DOI: https://doi.org/10.52793/ACMR.2022.3 (3)-35

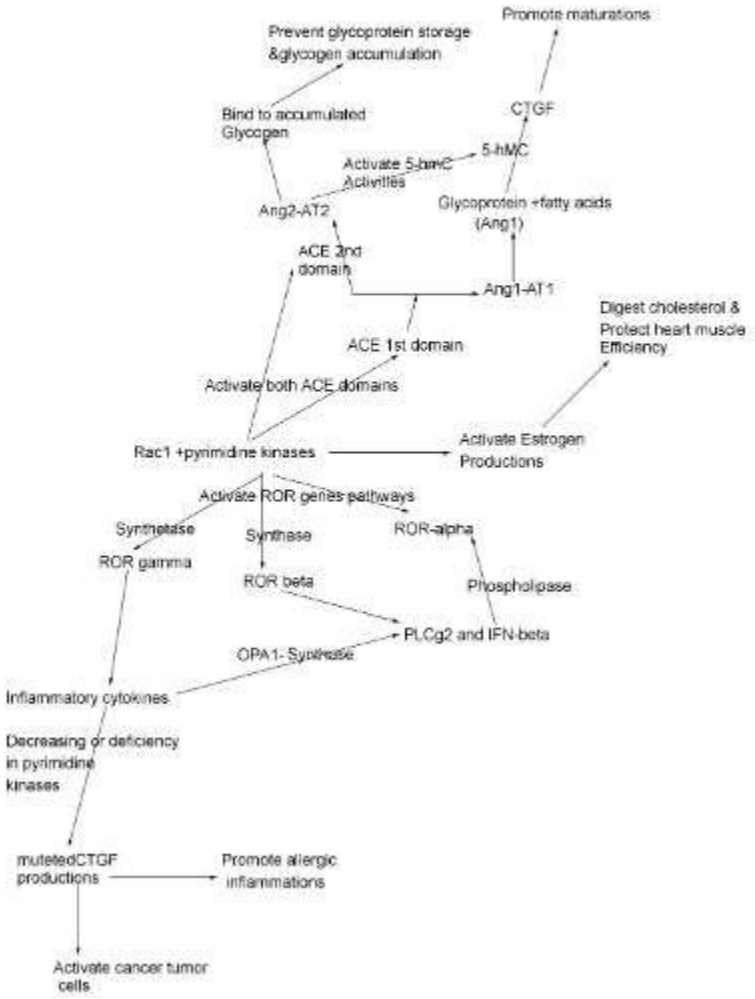

Figure 2: The roles Rac1 and pyrimidase kinases in activating ACE domains functions and the roles of pyrimidine kinases in promoting Estrogen productions and decreasing the cholesterol level.

I would like to note that, Phosphorylation of selected tyrosine Codons on receptor substrates is responsible to activate different pathways mainly 1st is Ang1-AT1 activities pathway,while the 2nd is Ang2-AT2 activities pathway, that Phosphorylation of selected tyrosine sites with TAA and TAG Codons will induce purines kinases that increase the glucose uptake which will reactivate S6K and ATP function and lipogenesis, while phosphorylation of TAT and TAC codons will increase the functionality and controlling the purines kinases activities and promote protein synthesis (glycoproteins) as well for the stimulation of cell growth, and adrenalin synthesis. The Tyr phosphorylation and active Rac1-rich-Proline is so necessary for genes synthesis and adrenalin through S6K productions which activate adrenalin by

converting Tyr and phenylalanine to adrenaline Molecules which stimulate increasing in the purines uptake for S6K and ATP activities. Also, Phosphorylated Tyr Codons (TAT, TAC, TAG, and TAA) will be needed for the Epinephrine synthesis which can activate hydroxy methyl-Cytosine that activates both CMs and endothelial cells activities mediated by Ang2-AT2 productions and ACE regulations.

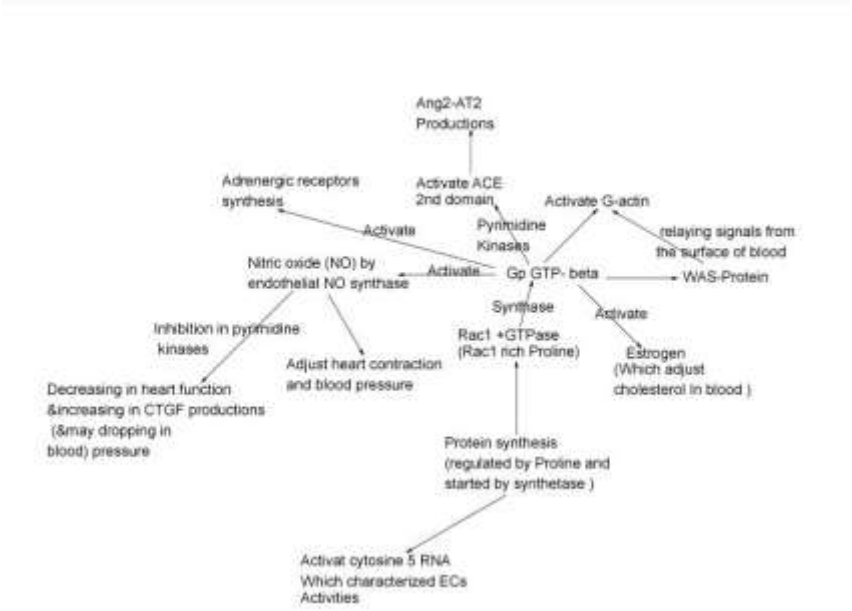

Figure 3: Necessity of Gp GTP beta Subunits in activating endothelial cells and CMs functions.

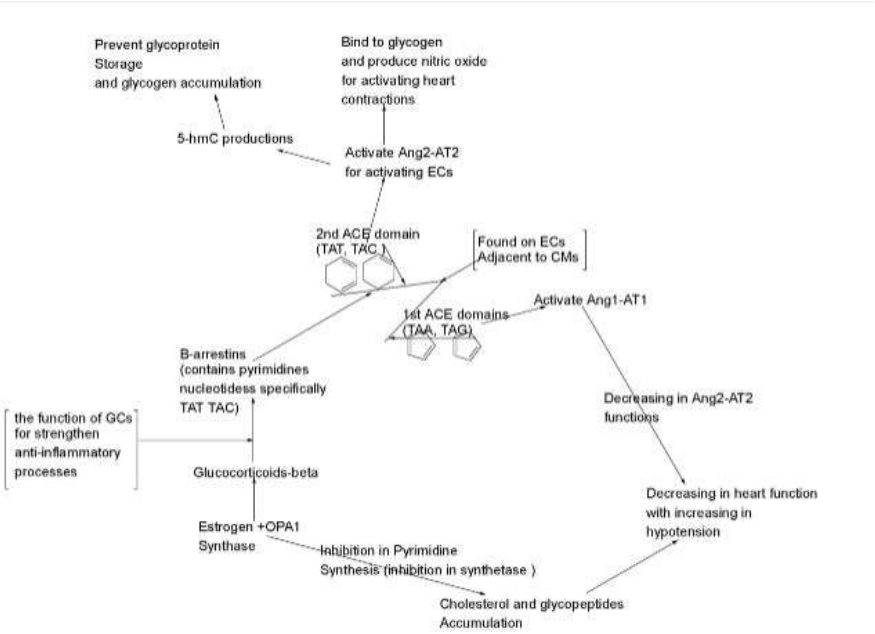

Figure 4: The function of glucocorticoids of B-arrestins productions regulated by OPA1 synthase enzymes for activating ACE 2nd domain for activating Ang2-AT2 for ECs functions.

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The necessary Tyr Codons TAT codons followed by TAC codons are necessary for building promoters in Ang2-AT2 (which considered as C-protein responsible for migrating molecules and adjusting signals for adjusting Myocardial contraction and relaxation) ، where the increase in protein C which contain Tyr TAC Codons can disturb the interstitium fluid processes due to stimulation the methylatiions and demethylations process which affect heart contractions. It is approved that the Angiopoietin-1 a Ligand for the TIE2 Receptor is required during Embryonic Angiogenesis [21]. Where, Tyr kinases (contains necessary Tyr Codons) are necessary for activating Angiopoietin-1 for modifying its own crucial roles throughout building the TAT and TAC in the Ang2-AT2 (Ang2-Tie2) molecules productions (regulated by ACE domains functions) in mediating reciprocal interactions between the endothelium and surrounding matrix. Ang2 is necessary to bind with Tie 2 to form Ang2-AT2 receptors expression (regulated by Tyr kinases) which are so necessary for adjusting heart contractions and efficiency that has the unique functions for preventing the deposition of glycoprotein and glycogen in blood vessels.and tissues.

That, Angiopoietin-1 (Ang1) binds to and activates endothelium-specific receptor tyrosine kinase "Tie2", that Ang1-Tie2 signal has been proposed to exhibit two opposite roles in the controlling blood vessels [22]. That the synthesis of Ang2-AT2 is upon the effect of Converting Enzyme ACE will activate two opposite Pathways:
The 1st is activating Ang1-AT1 production upon the effect of 1st ACE domain from Ang2-AT2 for activating CTGF for modulating CMs functions, while the 2nd is activating Ang2-AT2 from Ang 1 by the effect of 2nd ACE domain for activating ECs.

That indicated the necessity of tyrosine kinases (contained proper necessary Tyr Codons) in Ang1-Tie1 and Ang 2 Tie2 receptors synthesis for modulating Embryonic Angiogenesis for the heart beat adjustment and migrating molecules functions, but I note that Tie 2 receptors kinases regulate endothelial activities through the availability of TAT and TAC Codons in Tie2 for Ang2 productions that appear is forming Ang2 Tie2 active molecules which are necessary for modulating heart activities and protecting blood vessels from accumulated cholesterol and glycoproteins. That, the migration and proliferation was significantly reduced in Tie2-deficient, and Tie2 ligand Angpt2 acts antiatherosclerotic, which is compatible with an antagonistic mode of action of Angpt2 on Tie2 [23]. Migration and proliferation was significantly reduced in Tie2-deficient which activated by ACE 2nd domain or can represent the ACE 2nd domain which contain tyrosine TAT and TAC codons only, which are so necessary for antiatherosclerotic (that Mast cells and heparin productions regulated by tyrosine kinases and BTK function, that there is an expect that ACE both domains have an interesting roles in heparin productions.

The necessary Tyr Codons TAT and TAC kinases (Tie2) are playing imp roles in building active promoters in heparin regulated by Ang2-AT2 productions which necessary for platelets activation through binding to glycogen and bind to stored glycoprotein that will prevent their accumulations, where Ang2-AT2 and heparin are connected in antiatherosclerotic activities, adjusting blood pressure and blood flow and raising the CMs activities followed by raising ECs functions. Where also it's expected that all Ang1-AT1, Ang2-AT2, and heparin are Regulated and modulated by the ACE functions. The availability of building the proper dynamic active promoter which formed from Tyr TAT and TAC Codons and pyrimidine kinases is the main basic controller for increasing the Ang2-AT2 activities. The abnormal expression of

angiopoietin 1 and endothelial cell tyrosine kinase receptor (Tie2) has also been reported in various malignant tumors, including papillary thyroid carcinoma (PTC), where high expression levels of Ang1 and Tie2 were observed in PTC tissues and cell lines [24]. That deficiency in pyrimidine kinases will lead to accumulation of purines that will build glycoprotein molecules with random compositions of purines with traces of pyrimidines that will reflect mutations in glycoprotein molecules in spite of can run proliferation by purines kinases activities.

The Tyrosine role is to form the basic dynamics promoter in Ang2-AT2 (the Ang 1 Tie2) molecules where the tyrosine has several codon 1_"TAT" which form the normal dynamic promoter in Ang2-AT2 2_ but "TAC" which form the Ang 2 and AT2 and carry imp functions for migrating molecules and activating hydroxymethyl Cytosine activate (which recover Ang1 and AT1 through ACE 1st domain functions). 3_"TAA" & "TAG" are responsible for building Ang1 AT1 for proliferation, (responsible for glycoprotein and collagen accumulation in arteries in case of deficiency in the Tyr TAT and TAC Codons "pyrimidine kinases"). Both tyrosine TAT and TAC codons are necessary for Ang2-AT2 synthesis where The Tyr TAT codon is necessary for activating the Ang 2 AT2 promoter synthesis while Tyr tax Codons are necessary for hydroxymethyl Cytosine activities which activated by endothelial cells activities which adjust heart beats contractions, that any deficiency or mutations in previous Tyrosine codons will be result of coronary artery diseases, heart diseases, tumor cancer, and allergic inflammations. Ang2-AT2 play a modulatory role in blood pressure and imp for adjusting anti-inflammatory processes, and antiatherosclerotic and reactivate blood flow, that play imp roles in protecting heart activities and blood flow and protecting from accumulated glycogen. Where, Glycoprotein VI is a major collagen receptor for platelet activation: it recognizes the platelet-activating quaternary structure of collagen [25]. That Glycoprotein VI contains excess percentage of Tyr "TAA and TAG" Codons are the majority of collagen content which upon Tyr kinase function contains Tyr Codons TAT and TAC (which promote Ang2-AT2, productions) will activate platelet activation upon phosphorylation processes, where the deficiency or decreasing in TAT or TAC Codons will reflect decreasing in platelets activations with glycogen accumulation.

Where activating proper Ang2-AT2 will activate the platelets activation that will adjust blood flow and will reflect increasing in endothelial cells activities, vascular remodeling, recovering the cellular damage, and adjusting Myocardial contractions and relaxations. Where, Rapid tyrosine phosphorylation and activation of Bruton's tyrosine/ kinases in platelets induced by collagen binding [26]. It's clear that phosphorylation by Tyr kinases (contains TAT and TAC Codons) are playing so necessary roles in platelet activation through Ang2-AT2 synthesis and bindings to glycogen in metalloproteinase dependent for platelet activation and prevent accumulation of glycogen which mediated by CpG productions, that will reflect increasing in blood flow and in heart contractions and functions. So, Ang 1 AT1 receptor are depending on Tyr kinases which contains Tyr "TAA and TAG " Codons for building Ang2 AT2 synthesis which need availability of Tyr TAT and TAC Codons for its productions for promoting platelets activation and activate proper ECs functions. The Ang1 AT1 needed for proliferation, where increasing in Tyr TAA and TAG Codons with relatively decreasing in Tyr TAT and TAC codons will activate glycogen synthesis and its accumulation.

Effect of ACE on Heart Failure and on Increasing Adverse Ventricular (LV) Dilatation

Angiotensin I-Converting Enzyme (ACE) are responsible for converting AT1 receptor to AT2 (where ACE responsible for forming Ang2-AT2 from Ang1-AT1 to be differ from each other according to availability of Tyr TAT and TAC codons in Ang2-AT2). AT2 will bind with Ang2 for activating normal necessary endothelial functions, where ACE consists of two catalytic domains and is found on the surface of endothelial and epithelial cells throughout the body. That as ACE consists of two catalytic domains located on the surface of endothelial cells as it looks to me that one of its domain "1st domain" contains Tyr TAA and TAG which can reactivate Ang1 synthesis, while the other 2nd domain contains the necessary Tyr Codons TAT and TAC which necessary for reactivating Ang2 AT2 from Ang1, That ACE "2nd domain" acts on AT1 for AT2 synthesis but it's main sits for acting are the phenylalanine and Tyrosine, where In cases of deficiency in 2nd domaine of ACE will be the result of Deficiency in AT2 and then reductions in migrating Molecules and consequently will lead to accumulation in glycogen in arteries and decreasing in platelets activation then in long term of decreasing in ACE 2nd domain with increasing in maturation by Ang1 will be the result of increasing in left vertical size and then dropping in blood pressure. Proper Ang2-AT2 has proper activities depending on proper tyrosine (TAT and TAC) kinase receptors functions, where both Ang1-AT1 and Ang2-AT2 acts as an antagonistic factor (anticoagulant) that Ang2-AT2 activate hydroxy methyl-Cytosine which increase methylation and demethylation that adjust heart contractions.

The two ACE domains are located on endothelial cells surface and adjacent to CMs cells that I consider it as sensor key that activate either of CMs or ECs (or both following eachother) depending on the receiving signals from interstatium fluid and from blood plasma where can strengthen anticoagulants by re- activating Ang1 AT1 through 1st ACE domains functions, or can strengthen Ang2-AT2 activities by 2nd domain functions which promote 5-hmC productions for increasing the migration functionality and prevent accumulated molecules which is another way of anticoagulants characters and functions. That The activating ACE2/Ang 1–7 results in beneficial effects to prevent heart disease and HF [27].

But stil the ACE2/Ang 1–7 depending on ACE1 (which consider as 1st ACE domain that contain the tyrosine TAA and TAG Codons to activate Ang1 AT1) to be evaluated to prevent heart disease through regulating Ang2-AT2 upon the effect of ACE 2nd domain (which contain the tyrosine TAT and TAC codons). Where, ACEI/ARB treatments can cause ACE2 upregulation with consequential beneficial effects considering either cardiovascular disorders or lung injury [28].

That ACEIs exert powerful nephroprotection and offer marked CV risk reduction in diabetic patients with concomitant [29]. Not only Angiotensin Receptor Blockers can Increase Risk of Myocardial Infarction but also decreasing in Tyr "TAT and TAC Codons" kinase and in pyrimidine kinases will reflect deficiency in ACE 2nd domain activities that can be the result of decreasing in Ang2-AT2 receptors. Productions that can form the Myocardial Infarctions and heart dysfunctions. Exciting new findings point to functions of the AT1 receptor related to growth and vasoconstriction (mediated by c-Src or Fyn), transactivation by PDGF and Axl, and functions related to inflammation and migration (mediated by JAK, TYK, c-Src, and

FAK). Future work will be required to determine the nature of these different kinase pathways [30].

Synthesis of AT1 receptor are depending on ACE1 activities that related to growth and vasoconstriction that the roles of AT1 is running maturation and proliferation due to the AT1 contents from Tyr Codons TAA and TAG Codons, where in the cases of Deficiency in ACE 2nd domain which responsible for Ang2 AT2 productions (which regulate and control Ang1 AT1 activities) the Ang1-AT1 will activate the growth and vasoconstriction freely without the control from Ang2 AT2 (which suppose to be formed upon ACE2 activities) that will lead to accumulated glycoproteins. In cases of coronary artery inflammations the Cholesterol deposits (plaques) in the arteries (due to deficiency in estrogen synthesis which related to decreasing in pyrimidine kinases productions from Ser /Thr mTOR phosphorylation pathway that related to deficiency in Tyr TAT and TAC Codons) will activates cytokine receptors coupled to the Jak-Stat signaling pathway.

Deficiency in pyrimidine kinases reflect Estrogen deficiency that cause cholesterol accumulation increasing in the risk of coronary artery disease. Estrogen are thought that necessary to modulate coronary heart disease (CHD) risk. Estrogen synthesis regulated by pyrimidine kinases productions that has the role to promote citrate synthase productions via ROR pathway that synthase (CS) plays a critical role in providing citrate derived acetyl-CoA for lipogenesis and cholesterol genesis [31]. Where deficiency in citrate synthase "CS" will reflect deficiency in estrogen and then accumulation in cholesterol which will drop aorta endothelial cells activities "with regular activity in CMs maturation functions" lead to decreasing in pumping blood with increasing in EGF function that can lead to increasing in size of left ventricle.

Notice: dropping in estrogen synthesis will reflect dropping in Thymine and in cytosine kinase synthesis (pyrimidine kinases) which can produced from Ser/ Thr mTOR phosphorylation pathway [32] Pyrimidines kinases can ne obtained from Tyr TAT and TAC Codons required for ECs Ang2-AT2 synthesis that necessary for regulating heart contractions and blood flow in aorta.

Increasing in Ang1 which is glycoprotein family depending on presence of Tyr TAA and TAG cpdons and purines kinases productions from Ser /Thr mTOR phosphorylation pathway in deficiency in pyrimidine kinases will increase the risk of the size of the left ventricle. Also its good to note that pyrimidine kinases that produced from Ser /Thr mTOR phosphorylation pathway contribute in the synthesis of Tyr TAT and TAC Codons synthesis and promote the citric synthase production and will promote the Ang2-AT2 production upon activating ACE 2nd domain that activate the adjusting of heart contractions through activating endothelial cells.

That, there is convincing evidence that multiple interrelated immune mechanisms interact with metabolic risk factors to initiate, promote, and ultimately activate lesions in the coronary arteries. [33] Ang II increased CTGF production via AT1-R, which could be mediators of collagen synthesis by Ang II [34]. Ang II (upon ACE functions) activate Ang1-AT1 and consequently the CTGF production via AT1-R, which could be mediators of collagen synthesis (upon Tyr kinases activities which activate MAP and metalloproteinase for collagen digestions upon Ang2 AT2 binding that will promote platelets activation).

CTGF which activated by Ang1 AT1 for maturation can be reactivated by Ang2 AT2 too upon ACE 1st domain functions which reactivate Ang1 AT1 from its 1st domain which locate at surface of endothelial and epithelial cells.

Ang I and it's receptor are a main activator for CTGF production upon Tyrosine TAA and TAG Codons kinases functions (purines kinases) which is a mediators for collagen synthesis depends on the percentage of availability of TAA and TAG (related to the decreasing in TAT and TAC of Tyr Codons) which can accelerate the promoting of collagen biosynthesis which can be accumulated upon deficiency in Tyr TAT and TAC kinases Codons activities (where Tyr TAT and TAC codons activate Ang2 AT2 production (or we can say tyrosine TAT and TAC codons activate ACE 2nd domain functions). The CTGF produced by Ang 1 (regulated by Tyr kinases function or TrkA which serve as Tyr kinases) is a mediator for collagen synthesis which can be accumulated in blood vessels due to increasing in Tyr TAA & TAG codons related to the decreasing in Tyr TAT and TAC condones.

Where, It has been approved that: TrkA serves as a tyrosine kinase receptor for CTGF [35]. That Tyr TAA and TAG Codons (purines kinases upon phosphorylation) are the basis for producing CTGF from Ang1 that in case of decreasing in TAT and TAC of Tyr Codons (Pyrimidine kinases) will lead to decreasing in platelets activation with collagen and glycoprotein accumulation that will lead to decreasing in catabolic process (decreasing in hydroxymethyl-cytosine activities which related to Ang2-AT2 functions and related to pyrimidines kinases functions) that will reduce the synthesis of signals which responsible for adjusting heart contractions specifically in aorta that will give priority to purines kinases to activate CTGF to work freely for maturation that can cause increasing in left vertical size and will cause hypotension upon long term and heart failure depending on percentage of increasing in CTGF activities related to the deficiency in pyrimidine kinases. Also it's imp to note that the pyrimidine kinases (Thymine kinases and cytosine kinases) can be extracted and produced from Ser /Thr mTOR phosphorylation pathway upon availability of the Serine amino acids that can activate estrogen synthesis, the ACE and both Ang1-AT1 and Ang2-AT2 to protect heart and blood vessels in healthy conditions. But, Abnormal tyrosine kinase activity disturbs the physiological cell homeostasis and can lead to cancer, vascular disease, and fibrosis [36]. The abnormal Tyr kinases due to deficiency in TAT and TAC codons that lead to fully mutated Tyr kinases built by TAA, TAG, and traces of pyrimidine that upon accumulations can produce more gamma Cytokines "with increasing in AMP ATP" that will stimulate mutated CTGF production that increase inflammation due to mutated CTGF. Tyr Codons that needed for building imp promoter in Ang2-AT2 are the TAT and TAC codons which has roles of migrations and controlling Ang1 AT1 functions and purines kinases activities, but the codons necessary for CTGF production are the Tyr TAA and TAG Codons (and purines kinases) which are critical for proliferation and maturation.

The necessity of Hydroxymethyl Cytosine in CMs activities and in increasing heart muscles efficiency Hydroxymethyl Cytosine (where it's synthesis depends on pyrimidine cytosine availability) increase endothelial activities and CMs activities that responsible for increasing heart muscles efficiency throughout promoting the CpG production which can promote Ang 2 and AT2 synthesis (which depending on the cytosine kinases regulations) that will increase molecules migration and prevent the glycogen accumulation in intramyocardial arteries where glycogen accumulation will reflect decreasing

in Ang2-AT2 production. That, hydroxymethylcytosine in the genome is reported to be an intermediate of demethylation, that it has been suggested that the methylated CpG is actively hydroxylated during proliferation [37]. So, proliferation which run by Ang1 AT1 functions is mediated by Hydroxymethylcytosine activities which expected to be activated by Ang2-AT2 endothelial activities. The availability of cytosine is necessary for promoting Hydroxymethylcytosine synthesis (regulated by Tyrosine pyrimidine kinases) which is the same pyrimidine kinase that needed for ACE 2nd domain activities and for Ang2-AT2 productions which is necessary for preventing the accumulation of glycogen through promoting the CpG synthesis (from glycoprotein) that will activate the molecules migrations and prevent accumulated molecules. Also, the fail of methylation and demethylation processes will reflect deficiency in signals created (for adjusting heart contraction), also reflect failing in the migration of molecules and failing in CpG production which reflect decreasing in Ang2-AT2 productions that will lead to accumulated in fatty methylated Molecules and accumulation in glycopeptides that lead to decreasing in heart efficiency.

5-hmC which depend on the pyrimidines cytosine which build from necessary Tyr "TCA" condone are the enhancers and are key regulators for Ang1 AT1 activities and for heart development and contractions, where it has been approved that 5-hmC defines a subset of enhancers with increased activity enhancers are key regulators of tissue-specific gene expression programmes and in heart development and contractions [38]. And, DNA hydroxymethylation controls cardiomyocyte gene expression [39]. But, increasing in purines with deficiency in pyrimidine synthesis (due to deficiency in synthetase) can be results for Ang1 AT1 accumulation and Glycoprotein storage with Glycopeptide accumulations that will lead to increasing in cAMP upon activating the phosphorylation on purines in the Tyr TAA and TAG Codons that built Ang1 AT1 that will be the results of increasing in Ang1 AT1 proliferative activities and lead to cardiac hypertrophy and tissue fibrosis due to increasing in proliferation with inhibition in migrating molecules (due to deficiency or altering in pyrimidine in Tyr TAT TAC Codons which responsible for building Ang2-AT2), where, it has been approved that Chronic activation of the cAMP pathway by catecholamines results in cardiac hypertrophy and fibrosis [40]. That the excess activity of the cAMP pathway due to increasing in Purines kinases (increasing in Tyr TAA and TAG kinases too) with decreasing in pyrimidines kinsses will increase catabolic process with increasing in mutated CTGF productions that will increase glycoprotein and glycogen accumulations with deficiency in 5-hmC (which activated n'y pyrimidine kinases) and with decreasing in platelets activations that will lead to in cardiac hypertrophy and fibrosis. Fibrosis started by glycoprotein and glycogen accumulation with sever decreasing in pyrimidine kinases which responsible for activating 5-hmC (contain CACCC, CCA, or CAC boxes) that has the roles of migrating molecules and creating signals that adjust contractions.

Also, présence of CACCC boxe can activate the efficiency and mobility of genes that increase genes-binding eg running methylation and demethylation, and stimulating Insulin-like growth factor-binding protein-5 (IGFBP-5) gene activity mediated by CACCC-binding factors. Where, PG may stimulate IGFBP-5 gene transcription via a novel mechanism involving PR and CACCC-binding factors [41]. Previous study indicated the necessity of 5-hmC (regulated by pyrimidine kinases) in migrating molecules and in preventing cholesterol accumulation through estrogen productions (which is pyrimidine kinases dependent), where estrogen synthesis is promoted by pyrimidine kinases productions which is so

necessary for digesting cholesterol for preventing its accumulation and then promote RORs pathway that protect heart functions, where it has been approved that code for steroid receptors and enzymes associated with estrogen synthesis and metabolism in endometriosis [42]that steroid receptors, and enzymes synthesis are all pyrimidine kinases-dependent which is necessary for Estrogen synthesis.

And also, DNA methylation and hydroxymethylation levels in PR isoform promoters are not affected by estradiol treatments [43]. That, hydroxymethylations and demethylation are dependent on cytosine pyrimidine kinases which activate 5-hmC, and also estrogen are pyrimidine kinases dependent that will not affect on decreasing in 5-hmC activity but can have the roles of enhance its functions. So, it's clear that pyrimidine kinases which promote tyrosine TAT and TAC kinases are so necessary for estrogen productions (instead of androgen which promoted by purines kinases), where estrogen reflect the survival of Hydroxymethylations and demethylation by Hydroxymethylcytosine "5-hmC" which promoted by the pyrimidine kinases and contain cytosine box (CACCC or CCA..) that reflect the proper activity of migrating molecules and activating both ACE 2nd domain and Ang2-AT2 which enhance endothelial cells proper functions for protecting heart and blood vessels from glycoprotein, glycogen, and from Cholesterol accumulations.

The Tyrosine TAT and TAC kinases are necessary for activating Ang2 AT2 production and Hydroxymethyl-Cytosine activities (upon ACE 2nd domain functions) which is necessary for activating ECs functions throughout methylation and demethylation activities which create necessary signals that adjust Myocardial contractions and relaxations (where relaxation upon Ang1 AT1 activities that can be controlled by Ang2-AT2 functions through adjusting muscles contractions).

The Ang2 AT2 are formed from Ang1 AT1 upon tyrosine kinases functions and ACE functions which both basically regulated by proper BTK activities, that the primary Ang 1 protein formed in liver regulated by BTK synthesis which is imp for proliferation and important for IgM and IgG3 levels in the serum [44]. The primary Ang 1 protein which formed in liver is basically regulated by BTK function which responsible for building TAA and TAG Codons "purines kinases" in Ang1 molecules upon phosphorylation (where, Ang1 responsible for IgM and IgG3 levels), but second step is activating Ang2-AT2 synthesis upon ACE 2nd domain and Tyr kinases (which contains TAT and TAC codons) for activating endothelial cells activities for adjusting Myocardial contractions and relaxations and preventing the accumulation of glycoprotein, glycopeptides, and glycogen in blood vessels.

Pyrimidines kinases function are protecting from glycoprotein storage and from cirrhosis through the availability of the necessary tyrosine kinases "TAT and TAC kinases" in building Ang2-AT2 where its synthesis are so imp for preventing accumulated glycoprotein (where the decreasing in pyrimidine kinases will reduce its migration activities and will reduce controlling Ang1 AT1), that will lead increasing in mutated CTGF that will be critical for tumor proliferation and cancer cells due to availability of purines TAA and TAG and mutated triplets in producing CTGF for maturation, where BTK is still so imp for producing kinases for beta cells maturation and survival.

Ang1 with their AT1 receptor activated by specific types of Tyr kinases "purines kinases" are so

necessary for recoverimg the CMs activities "which controlled by ECs functions". Heparin reactivate ang1-AT1 receptor and its intracellular signal transduction that as necessary Tyr cordons changed in heparin as will be the reasons for allergic inflammations and more:
First, the Mast cells are an important source of heparin "called glycosaminoglycans (GAGs)" found as sulfated polysaccharide, where, It is clear in this study that the tyrosine phosphorylation status is critical for the ability of antigen to induce mast cell activation and for SCF to modify this response [45].
So, firstly Tyr kinases is the main regulator for providing mast cells with the needed nucleotides kinases (purines or and pyrimidine kinases) for their cactivities and heparins productions. That Ang1 and heparin are the basic activator for epidermal growth factor receptor "EGFR", where Ang II activities in a specific pathway will promote processing of pro–HB-EGF [46] in specific pathway from Ang1 (upon renin function) in a metalloproteinase-dependent manner to stimulate maturation.

How Ang1 in metalloproteinase dependent stimulate maturations?
Answer: Stimulation of receptor tyrosine kinases results in the regulation of mitogen-activated protein kinase "MAP" kinase signaling cascades which may play an important role in dictating other cellular responses such as metalloproteinase expression [47]. So, as proper Tyrosine kinases activated as metalloproteinase will activate collagen digestion upon Ang2 AT2 binding which will reactivate Ang 1 (upon ACE 1st domain effect) to activate proliferation mediated by Connective Tissue Growth Factor Gene Expression "CTGF" productions and platelets activations, that previous pathway basically depends on proper tyrosine kinases activities containing proper TAA and TAG Codons which form purines kinases for ETGF production and TAT, TAC codons which form pyrimidine kinases necessary for Ang2-AT2 productions for adjusting heart muscles contractions and protect blood vessels from cholesterol and from accumulated glycoproteins.

That it has been reported that Ang II transactivated EGFR via AT1, and inhibition of EGFR abolished the induction of Ang2, that Ang II caused processing of pro–HB-EGF in a metalloproteinase-dependent manner to stimulate maturation [48]. The Ang II transactivated EGFR via AT1, but induction of Ang2 AT2 is abolished by delaying or control EGFR production for preventing the storage of glycoprotein and glycogen in metalloproteinase dependent (through binding to Ang2-AT2) for platelets activation and recover Ang1 and re-adjustment the heart contractions. Also, indicate that heparin promote the growth factor EGFR productions from Ang1 where Ang2-AT2 synthesis can reduce or control EGFR production for stimulating the pro-HB-EGF synthesis in another pathway from Ang1 AT1 (and platelets activation mediated by metalloproteinase and Ang2-AT2 binding). So, heparin is an imp activator and recovery for glycopeptides and glycoprotein synthesis that recover the primary Ang1 molecules which upon specific proper Tyr kinases functions will activate Ang2-AT2 for complete adjustment of heart function and blood vessels protection from accumulated glycopeptides.

In another meaning heparin is a main stimulator for glycoprotein (Ang1)synthesis which upon Tyr kinases (contain TAA and TAG Codons) function will activate the purines kinases phosphorylation and stimulate cAMP and GTP productions which will activate growth factor (pro–HB-EGF) synthesis to induce maturation in one pathway but in other pathway the pro–HB-EGF can be formed due to the Ang2-AT2 activities for collagen binding and digestion (metalloproteinase dependent) for platelets activation and

then Ang1 AT1 but with will re-produced upon ACE functions for EGFR productions for maturation.

That Tyr Codons (TAT, TAC, TAA, TAG) are so necessary for activating mast cells and their heparin Productions, but it's clear to us that Tyr TAT Codons are necessary for building active promoter in active genes and subunits, where Tyr TAC Codons are imp for C-protein for promoting migrating molecules and perform catabolic process for adjusting anti-inflammatory processes [49]. And, This study demonstrated that heparin recovered Ang receptors [50]. Now It's expected that heparin can enhance the Ang1 recovery and Ang1-AT1 upon phosphorylation, but heparin cannot activate protein kinase C, where it has been demonstrated that Inhibition by heparin of protein kinase C activation and hydroxyl radical generation in puromycin aminonucleoside treated isolated rat hepatocytes [51]. As heparin inhibit protein C kinases as it can reduce or inhibit Ang2-AT2 activities that can reduce blood pressure in hypertension or can lead to hypotension depending on the percentage of decreasing in Ang2-AT2 activities. That It has been reported that Heparin lowers blood pressure and vascular calcium uptake in hypertensive [52].

In Conclusion of Heparin Activities

Heparin can recover Ang1 AT1 (upon phosphorylation) but can inhibit pyrimidine kinases function, so heparin (in cases of sever deficiency in pyrimidine kinases) can enhance decreasing in a Ang2-AT2 activities, and decreasing in pyrimidine kinases activities, that can lead to cholesterol accumulation, glycoprotein accumulation,, hypotension ، Atherosclerosis, osteoporosis, and leukemia (depend on the percentage of decreasing or inhibition of pyrimidine kinases in one or in more that one tissue), where heparin can enhance Inhibition or modulation of keratinocyte growth and adherence and can also binds and potentiates the growth-inhibitory function of TNF-alpha (Which contain mutated CTGF). And can increase regular catabolic processes by increasing in ATP activities that potentiates only purines activities and their catabolic processes by increasing ATP activities. Note,, it's dangerous for many pathogenic cases to use Heparins as anticoagulants where it is widely used as anticoagulants in clinical practice, and is known to provoke all types of hypersensitivity processes. That As Tyr cordons changed in heparin molecules may reflect mutations in BTK pathways and in Tyr purines kinases function that can lead to allergic inflammations or to tumor in cancer.

Heparins are widely used as anticoagulants in clinical practice, and they are known to provoke all types of hypersensitivity reactions; especially delayed type hypersensitivity reactions [53]. Also, if Tyr cordons changed in heparin molecules it could be the main reasons for Reverse the heparin functions and can cause maturation of allergic inflammatory growth. That the L99F mutation of AT is associated with destabilization of the serpin structure and that the loss of anti-inflammatory signaling function and may also contribute to enhanced thrombosis in carriers of HSB mutations [54].

AT1 is considered as anticoagulants the same as heparin where the main secret point of stimulating Thrombosis is the decreasing in purines kinases which main for both AT1 and heparins (related to the availability of pyrimidines kinases which are basis for building Ang2 AT2), so the HBS variants of AT (AT-I7N and AT-L99F) (the variant concluded decreasing with variation in TAA and TAG sequences in AT1 binding), will be associated with higher incidence of Thrombosis. And also decreasing in pyr kinases and

in Ang2-AT2 activities can reflect accumulation in glycoprotein and may lead to mutation in CTGF that can enhance allergic inflammations maturation and growth in Cancer cells, and can enhance the increasing in left vertical size and hypotension cases. Heparin recovers AT1 receptor and its intracellular signal transduction in cultured vascular smooth muscle cells [55]. Also, G-prorein and heparin-binding epidermal growth factor-like growth factor (hbEGF), stimulated bovine satellite cell proliferation [56].

That, heparin mainly depends on purines in its synthesis that can activate proliferation (mediated by CTGF) upon Tyr purines kinase functions that will activate AMP productions, but heparin excessive activities should be controlled by Ang2-AT2 prodctions and activities. As ACE two domains located on the surf of endothelial and epithelial cells that has the roles of adjustment and activating both ang1 AT1 and Ang2-AT2 and as heparin can inhibit keratinocyte growth, As it looks to me that heparin can inhibit or minimize only the ACE 2nd-domain functions on epithelial cells that can inhibit keratinocyte growth, where it has been reported that heparin not only inhibits or modulates keratinocyte growth and adherence but it also binds and potentiates the growth-inhibitory function of TNF-alpha [57]. Where deficiency or decreasing in Ang2-AT2 functions can enhance the evasoconstriction, glycoprotein storage, and glycogen accumulation (depending on percentage of Tyr TAT and TAC Codons deficiency) that cause hypertension. Cell division control protein "Cdc42 " which mediated by Tyr phosphorylation pathway and then mediated by Gp-GTP-gamma followed by Gp-GTP-beta production (upon synthase effect) that will be result of creating oxidative signals migrations that activate Cdc42 productions which is the main regulators to CMs and then to ECs mediated by NO synthesis which is the main for creating signals charges which activate G-Actin functions.

That the Small GTPases (Gp GTP subunits) are the key to actin cytoskeleton signaling, which opens the lock of effector proteins to forward the signal downstream in several cellular pathways [58]. As the active Gp GTP subunits carrying specific designed hydrophobic acids in G-prorein that regulated by Rac1 for activating CMs and endothelial cells (through Inheriting active G protein for activating endothelial cells), as changing in the characteristics of the Inherited amino acids in the G-protein from Rac1 can be considered as a sign of dysfunction in both CMs and ECs functions and can reflect decreasing in heart functions.

That Gp GTP-beta subunits are the main key for activating G-actin that can enhance sending and receiving signals from adjacent cells and tissue and are carrying the main anti-inflammatory roles that protect tissue cells and epidermal cells and through sending signals can stimulate the two ACE domains functions for recover Ang1-AT1 and Ang2-AT2 synthesis. The previous Gp GTP subunits activities are reflecting the necessity of Rac1 as playing a necessary connective roles and activities between Wasp (where, WASP-homology 1 domain interacts with poly-Proline) activation and chemo-attractant stimulation in the signaling pathway regulating F-actin assembly during chemotaxis, as indicating the necessity of proline in Rac1 molecules for adjusting blood pressure (adjusting lwo blood pressure) and Myocardial contractions and relaxation through promoting the Gp GTP subunits synthesis mediated by pyrimidine synthesis and amino acids synthesis (regulated by aminotransferase), where Gp GTP subunits are necessary for Adrenergic receptors synthesis which are necessary for Cardiomyocytes (CMs) and endothelial cells (ECs) reactivities through activating both Plcγ2 and IFN-beta which can be considered as

the necessary productive processes for CMs and ECs activities mediated by interactive steps with WASP protein mediating the actins activation.

WAS-Protein is involved in relaying signals from the surface of blood cells to the actin cytoskeleton regulated by Rac1 and mediated by Gp-GTP-subunits productions (gamma, beta and alpha) which necessary for regulating PLCγ2 and IFNs synthesis followed by TXA2 synthesis for blood cells synthesis which carry WAS-proteins on their surface for relaying signals which basically created by Rac1-rich-Proline functions through activating endothelial cells. In fat metabolism, The fatty Acyl-COAs synthesis (upon OPA1 enzymes regulations) are the important steps for regulating and activating CMs and ECs Notice that the excessive lipids are taken up by cardiomyocytes will lead to cardiomyocyte dysfunction and death, where that phenomenon is known as lipotoxicity. That estrogen-related receptor (which main productive molecules promoted by fatty Acyl-COAs productions) is known to regulate a wide range of gene expression in cardiomyocytes, including β-oxidation of FA, oxidative phosphorylation, and contractile proteins [59].

Also, Notes, the generation of Gp GTP subunits is imp for Acyl-COA synthesis (specifically the Gp GTP beta subunits) regulated by OPA1 enzymes in FOX pathway where decreasing in Acyl-COA-beta synthesis will reflect decreasing in both go GTP bêta sublime and in both PLCγ2 and IFN-beta synthesis that will reflect decreasing in the CMs and in ECs activities and functions through dropping in G-actin activities.
In other clarity, increasing in blood sugar followed by Inhibition in proline activities (in Rac1 molecules) will decrease amino acids synthesis and in Tyr phosphorylase activities with accumulation of glutamate that inhibit transporting Acyl-COA to mitochondrial OPA1 that will lead to inhibition in OPA1 synthase oxidative processes (inhibition in signals derived by synthase and by phospholipase activities) that will lead to sharp decreasing in both CMs and in ECs functions (deficiency in Ang2-AT2 functions and in Gactin activities) that can lead to sharp drop in heart beats and in blood pressure. Where, Endothelial cells (ECs) are critical mediators of blood pressure (BP) regulation, primarily via the generation and release of vasorelaxants (reduction of vascular tension), including nitric oxide (NO) by endothelial NO synthase (eNOS) functions [60].

Where, the Loss of this specificity such as decreasing in NO delivery from ECs cells will be result of cellular disturbances and decreasing in heart activities and functions. cardiac NOS synthesis can draw on specific imp characterization of the cellular and molecular activities for anti-inflammatory effectiveness and mediated signals transmission production which necessary est cardiomyocyte bio-activities [61]. In vivo the nitric oxide produced upon inflammatory responses through the primary effect of synthetase on biological molecules or on protein-pyrimidine kinases for producing IFN-Gamma and PLCγ1 subunits which then directed to OPA1 synthase effect for nitric oxide productions, where previous OPA1 oxidative processes for NO production are carrying the main responsibility for signals or charges for creating heart beats and adjusting blood pressure. NO synthesis mainly regulated by pyrimidine-kinases synthesis, where the Partial inhibition of nitric oxide synthesis in vivo does not inhibit glucose production [62]. So basically the synthesis of pyrimidine kinases whether thymine or cytosine kinases where their synthesis basically is regulated by and depends on availability of Ser phosphorylations in the Ser/Thr mTOR phosphorylation pathway, that the inhibition of pyrimidine kinases synthesis will reflect

Inhibition in Ser amino acids phosphorylation and 5hen inhibition in NO synthesis which followed by dropping in blood pressure due to dropping in NO synthesis and reductions in IFN-beta and in PLCγ2 synthesis due to reductions in synthase functions which are fully depends on pyrimidine kinases synthesis and on the hydrophobic amino acids synthesis which regulated by Proline (in Rac1 active molecules) and by aminotransferase function. The productions of pyrimidine kinases are the main substrate in FOX pathway (regulated by OPA1 enzymes) for IFN-Gamma synthesis upon the effect of synthetase enz followed by the effects of OPA1 synthase enzyme for IFN-beta synthesis [63].

Also, pyrimidine synthesis (includes pyrimidine kinases) are so imp through are linked to protein synthesis, means the main function of synthetase enzymes is considered to be specified for pyrimidine synthesis that produce cytosine methylation where it has been reported that Cytosine-5 RNA methylation links protein synthesis to cell metabolism [64]. As the function of OPA1 synthetase is the pyrimidine synthesis necessary for Proline and for hydrophobic amino acids synthesis through the effect of synthase for RNAs (IFN-beta and PLCγ2) synthesis for increasing anti-inflammatory processes followed by phospholipase effects for producing IFN-alpha and PLC-alpha necessary for cells growth. As cytosine synthesis done as aminotransferase will be synthesis upon oxidative processes by synthetase to eliminate amino group for aminotransferase synthesis and cytosine-5 RNA methylation which will be involved and mediated in IFN-beta and PLCγ2 synthesis upon OPA1 synthase activities and functions. And it is so imp to note that the availability of cytosine synthesis is necessary to promote the nitric oxide, where it has been reported that Nitric Oxide-induced Deamination of Guanine [65].

So, it is clear to me that decreasing in cytosine synthesis will be the result of decreasing in NO synthesis that will lead to decreasing in ECs activities that will be the result of dropping in heart beats and in blood pressure. Also, the increase in retinal GS elicited by Cytosine arabinoside (Ara-C) Ara-C is achieved through mechanisms which are quite different from those involved in the hydrocortisone [66] that previous study indicates the importance of Ara-cytosine in activating glutamine synthetase, where the inhibition in cytosine will be result of glutamic accumulation that reflect failure in heart function and neuronal toxicity.But availability of cytosine 5 RNA will adjust the increasing in purines and in accumulated glycoprotein by acting on purines for producing nitric oxide which activate G-actin and release signals which adjust heart contraction and consequently blood pressure.

That Ara cytosine are carrying imp roles in activating ECs functions which can increase heart efficiency that can be quite different from those mechanism involved in the hydrocortisone roles activities. Cardiomyocytes (CMs) and endothelial cells (ECs) are two of the most abundant cardiac cell types that are playing imp central roles in both cardiac remodeling and Regeneration (controlled and regulated by tyrosine kinases (pyrimidine TAT and TAC kinases and purines TAA and TAG kinases) production and by proper active Rac1 rich Proline synthesis.

The heart is consisting of various cell types where are communicat with each other through direct cell-cell interactions and paracrine signaling, where signals originally promoted and regulated by the presence of Proline in Rac1 which regulate cytosine 5 RNA synthesis and adjust the nitric oxide productions that all will be result of activating both cardiomyocytes and endothelial cells function that

both can be activated from Gp GTP subunits synthesis which will promote the synthesis of both Plcγ2 and IFN-beta (where Plcγ2 are mediating TXA2 synthesis) and can activate WAS-Protein which can promote the G-actin activities.

Cardiomyocytes (CMs) has the main roles for producing Cdc42 through the production of PLCγ2 and IFN-beta for cells division which happen basically after or due to anti-inflammatory responds which promote and activate both T-cells modulations macrophages functions, and promote B-cells maturation too.

Endothelial cells have been shown to have an important role in calcific aortic valve disease. As observed in atherosclerosis, ECs exposed to mechanical or shear stress become dysfunctional, with increased lipid deposition and immune cell infiltration, that Alteration of EC gene expression is an early event in vascular disease and plays a critical role in its progression [67].

So, inhibition in proper Rac1 synthesis due to inhibition in Proline, in Tyr, and other necessary hydrophobic amino acids will lead to alterations in Rac1 Molecular structures and activities that will affect in the alterations of ECs gene expression and will lead to vascular diseases.

Neuropilins (NRPs) are non-tyrosine kinase cell surface glycoproteins expressed in all vertebrates and widely conserved across species. The two isoforms, such as neuropilin-1 (NRP1) and neuropilin-2 (NRP2), mainly act as coreceptors for class III Semaphorins and for members of the vascular endothelial growth factor family of molecules and are widely known for their role in a wide array of physiological processes, such as cardiovascular. Neutrophil are formed from Gp GTP subunits specifically beta and alpha for generating both PLC beta and alpha and IFN beta and alpha responsible for cells division, activating T-cells, and NRPs are expressed in various subsets of immune cells important for regulating immune response [68].

Active Cdc42 improved coordination between actin filaments and microtubules and enhanced formation of vascular cords, suggesting that active Cdc42 rectifies defects in angiogenesis by improving cytoskeletal dynamics and capillary morphogenesis [69]. It has been reported that increased fibrinogen is a powerful predictor of stroke. Results did not disclose a differential relation with fatal or non-fatal stroke, or with type of stroke (ischaemic or haemorrhagic) [70].

Fibrinogen is a glycoprotein complex, produced in the liver, that circulates in the blood of all vertebrates. During tissue and vascular injury, it is converted enzymatically by thrombin to fibrin and then to a fibrin-based blood clot. Where, Thrombin is a multifunctional serine protease (notice that the reduction or inhibition in Ser protease due to inhibition in Ser and due to inhibition in PSTTk and PSTCk synthesis will reflect diabetes and inhibition in hydrophobic synthesis and reflect reduction and inhibition in Proline synthesis and activities and will reflect reduction or inhibition in fibrin synthesis and in accumulation in Fibrinogen) which plays a central role in haemostasis by regulating platelet aggregation and blood coagulation. It is formed from prothrombin and converts fibrinogen to fibrin due to injury. Those fibrinogen molecules are comprised of two sets of disulfide-bridged Aalpha-, Bbeta-, and gamma-chains.

Conclusion

Inhibition in the active specific type of Tyr kinases synthesis which contains the Tyr Codons TAT (imp for building its promoter) and TAC Codons (necessary for building active Ang2-AT2 glycoprotein) and in specific BTK function (which regulated by the same Tyr Codons TAT and TAC) will be result of accumulation of inactive Ang2-AT2 which considered as glycoprotein that will activate accumulation og collagen in arteries and will be result of inhibition in platelets activation (mediated by glycogen receptor binding) and accumulation of collagen on arteries wall and will be result of dropping blood pressure that can lead to heart failure and stroke. Collagen accumulation reflect Inhibition or reduction in platelet activation from Ang2-AT2 (which considered glycoprotein) where platelets activation regulated by specific Tyr kinase (contains TAT and TAC Codons) and collagen receptor binding.

GSD I is associated with arterial dysfunction evident by increased IMT and augmentation index. Patients with GSD I may be at increased risk for cardiovascular disease. The increasing in adverse ventricular (LV) dilatation will lead to increasing in Myocardial relaxation time that will be main reason in hypotension which due to increasing in ventricular size leads to an increase in the diastole of the heart due to increasing maturation and proliferation by Ang1 AT1 related to decreasing in Ang2-AT2 functions that lead to Vascular blockage and vasoconstriction and arrhythmogenecity that (depend on the percentage and type of Ang2-AT2 inhibition) may lead to sudden cardiac arrest due to the absence of the Tyr codons necessary for generating its needed charges upon phosphorylation by Tyr kinases.

Proper Ang2-AT2 has proper activities depending on proper tyrosine (TAT and TAC) kinase receptors functions, where both Ang1-AT1 and Ang2-AT2 acts as an antagonistic factor (anticoagulant) that Ang2-AT2 activate hydroxy methyl-Cytosine which increase methylation and demethylation that adjust heart contractions.

The two ACE domains are located on endothelial cells surface and adjacent to CMs cells that I consider it as sensor key that activate either of CMs or ECs (or both following eachother) depending on the receiving signals from interstatium fluid and from blood plasma where can strengthen anticoagulants by re- activating Ang1 AT1 through 1st ACE domains functions, or can strengthen Ang2-AT2 activities by 2nd domainfunctions which promote 5-hmC productions for increasing the migration functionality and prevent accumulated molecules which is another way of anticoagulants characters and functions. But notice if only the 1st domain work for activating only Ang1-AT1 will be the main reasons for increasing in left vertical size, and increasing in the accumulated glycoprotein and glycogen. But if only the 2nd ACE domain worked will be result of hypertension with sever decreasing in CTG-Factor and in ATPase function which depends on purines kinases and on S6K productions.

Both Ang1 AT1 and Ang2-AT2 functions are so necessary for cells survival and protections that any variation in AT1 concluded decreasing and variations in their purines sequences can be main for losing their anticoagulants functions and lose of anti-inflammatory characters, where Ang1-AT1 are the basic units for Ang2-AT2 producions regulated by the two ACE domains that any decreasing and variation in Ang1-AT1 will affect in the character of functions of Ang2-AT2 activities. Availability of cytosine 5 RNA

will adjust the increasing in purines and in accumulated glycoprotein by acting on purines for producing nitric oxide which activate G-actin and release signals which adjust heart contraction and consequently blood pressure.

That Ara cytosine are carrying imp roles in activating ECs functions which can increase heart efficiency that can be quite different from those mechanism involved in the hydrocortisone roles activities.
It is very important to. Recommend that pharma has to start to study this article very well and then start to prepares Tyrosine condos separately (Tyr pyrimidine Codons: TAT and TAC together as pyrimidine kinases, but Tyr purines Codons: TAA with TAG together as urines kinases) from different sources of plants, wild animals and different marines sources, that may one or some of them will be effective for treatment the vasoconstriction and weakness of the heart muscle and some can be effective to restore the size of the ventricle in a way where it was in normal size and natural conditions or strengthen its tissue for better heart contractions and optimal blood pressure.

This study is considered as aj understandable steps for next successful steps in the massive change in the methods of treatment of sclerosis thrombosis diseases, and in treatment heart diseases. That this study can be an important and powerful step in understanding how ACE domains mechanisms works in in adjusting both Ang1-AT1 and Ang2-AT2 levels and percentages for increasing the efficiency of endothelial and CMs cells activities, and It can be useful in a success for how to treat hypotension, atherosclerosis, accumulation of glycogen and glycoprotein, and dilatation in left ventricular size.

Conflict of Interest Statement

The Author declares 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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