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GCs-beta and B-arrestins Regulate Nrf2 via NR4As Productive Pathway Mediated by B-adrenergic for Anti-inflammation and Adopting Myocardial and Immune Functions

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ABSTRACT

The nuclear receptors "NR4As" productive pathway is the so important pathways for activating classic estrogen receptors and are important for regulating the adopted cellular anti-inflammatory growth (mediated by glucocorticoids, Nrf2, Ang2-AT2, and VEGF-A synthesis)which considered as the basic for B-arrestins synthesis which adopt B Adrenergic, and Nrf2 synthesis, that Nrf2 is strong activator to ACE functions for promoting Ang2-AT2 and VEGF-A synthesis for running the adopted anti-inflammatory growth and heme oxygenase.

The modulation of oxidative stress will be done by serotonin synthesis (regulated by tryptophan "TGG") which will promote melatonin synthesis which necessary to activate glucocorticoids productions via NR4A2 pathway followed by B-arrestins and Nrf2 productions for activating Ang2-AT2 and VEGF-A productions. That melatonin synthesis will be associated with GTPase production which promote and activate OPA1 repairs and functions, and responsible for activating glutamine synthesis which stabilize Leu functions through Nrf2 functions.

This study concluded that NR4As productive pathway are the important pathway for improving anti-oxidation through improving IL6 productivity to IL17 productions, and is important for glucocorticoids-beta synthesis followed by B-arrestins productions which activate B Adrenergic synthesis that are necessary for activating Nrf2 production that followed by activating ACE for Ang2-AT2 and VEGF-A synthesis for running anti-inflammatory growth, modulating antioxidative stress, activate heme oxygenase, modulating brain function and memories growth , and activating T-cells and B-cell functions.

That NR4As exert multilevel regulations of brain function and cardiac functions that protect immune survival from vascular cardiac diseases, and are the primary modulator to pro-inflammation and stimulator for variety of active genes and subunits started by estrogen and GCs-beta productions which followed by activating B-arrestins which activate B Adrenergic synthesis which has the roles of activating Nrf2 productions for adopting antioxidative functions, heme oxygenase, vasoconstriction functions, and anti-inflammatory growth mediated by Ang2-AT2 and VEGF-A synthesis.

NR4As pathway has the role of improving cytokines which produced by cDC2s for producing IL6 which improved to IL17 synthesis (upon synthase function and availability of glutamine for supporting Leu synthesis and functions) which necessary for modulating GCs-beta synthesis followed by both B-arrestins synthesis and B Adrenergic then followed by Nrf2 productions, (note 'N-Acetyl Serotonin activate Nuclear Factor Erythroid 2-Related Factor 2 for Alleviating Oxidative Damage mediated through promoting glutamine synthesis for activating Leu necessary for Nrf2 functions) then followed by activating Ang2-AT2 and VEGF-A necessary for anti-inflammatory growth for T cell functions and B-cell functions (that MZ B-cells which characterized by NR4As expression possess a strong.

B-cell regulatory functions are the main activator to glucocorticoids, to B-arrestins, and to Nrf2 production for activating Ang2-AT2 and VEGF-A synthesis). Also, this study concluded that β3-adrenergic receptors has important roles for preventing myocardial fibrosis by modulating antioxidative function through activating Nrf2 synthesis that B-adrenergic regulated by B-arrestins via NR4As productive pathway for activating Nrf2 production, that NR4As is a very important pathway for modulating oxidative stress (starred by the stimulation and modulation by serotonin followed by melatonin) for protecting heart, brain and liver functions from oxidative damages and from irregular proliferation activities. Also the β3-adrenergic responsible for lipolysis,and has the role of adoptung both anti-inflammatory growth and antioxidstive processes through activating Nrf2 synthesis followed by activating Ang2-AT2 and VEGF-A productions via NR4As productive pathway (where NRF2's has imp role is modulating stress response that can now be revised to be included the regulation of the basic functions of stem cells), that NR4A2 pathway can be concluded to:-
Pro-inflammation +NR4As ¬¬>IL6 ¬>IL17 (upon synthase function) ¬¬>activate GCs-beta ¬>¬>B-arrestins¬¬> B Adrenergic ¬¬>Nrf2 synthesis ¬¬>activate ACE functions ¬¬>activate Ang2-AT2 and VEGF-A synthesis ¬¬>anti-inflammatory growth, modulating antioxidative processes, activating heme oxygenase, and activating B-cell and T-cells functions.

The Inhibition in NR4As productive pathway will inhibit GCs-beta, B-arrestins, B adrenalic and Nrf2 synthesis that will be the main reason for Atherosclerosis (which can concluded Deficiency in Tph, Glu, and Leu functions).

Also melatonin synthesis which promoted by serotonin (regulated by Tph TGG) protect OPA1 repairs and functions through GTPase synthesis, and promote NR4As productive pathway for promoting GCs-beta productions and consequently prevent Lipids accumulation by increasing lipolysis followed by B-arrestins synthesis and Nrf2 productions.

The serotonin roles Is supporting the function of antioxidants through promoting melatonin synthesis (and producing GTPase for OPA1 repairs) which

promote GCs-beta synthesis which activate Nrf2 synthesis via NR4A2 pathway mediated by both B-arrestins, B Adrenergic, which activate ACE for activating Ang2-AT2 and VEGF-A synthesis for running anti-inflammatory growth.

Where inhibition in melatonin and in Nrf2 function can be the main reason for reducing GTPase functions and the visual memory deficits. And in conclusion the adoption of oxidative stress will be start by serotonin synthesis which will activate melatonin synthesis that will activate glucocorticoid-beta synthesis via NR4As pathway then the glucocorticoid-beta will activate B-adrenergic synthesis which will activate Nrf2 production "respectively" :-

The tryptophan "TGG" are necessary for activating serotonin which activate melatonin ¬>that will activate both glutamine synthesis (necessary for Leu synthesis for Nrf2 synthesis) and glucocorticoid-beta synthesis via NR4As ¬> where NR4As will promote estrogen from 17β-estradiol-mediated GPR30 activation ¬>then will activate GCs-beta¬> B-arrestins¬> B (2) -Adrenergic¬>
Nrf2 ¬> Ang2-AT2 ¬> VEGF-A ¬> anti-inflammatory growth ¬>heme oxygenase ¬¬>adopt antioxidative functions ¬¬>adopté T-cells functions… etc.

Tryptophan (Tph "TGG") are necessary for modulating oxidative stress and both brain and heart functions through activating serotonin synthesis which activate melatonin productions, and the Tph is necessary for activating glutamine synthesis which stabilize Nrf2 functions through activating leucine synthesis.

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Keywords: Nuclear Factor-E2-Related Factor 2 (Nrf2), Secreted Allergen-Specific IgE by B Lymphocytes, T-cells, Nuclear Receptors NR4As, Estradiol, Estrogen, Glucocorticoids, The B-Arristin which is a Nuclear Magnetic Resonance or β-arrestin2 Biosensors, B-Adrenergic, Nuclear Factor Erythroid 2-Related Factor 2 "Nrf2", Angiotensin2, VEGF-A, Tryptophan (Tph TGG), Glutamine (Gln GAA, GAG), Leucine (Leu "CTC, CTT"), Serotonin, Melatonin

Introduction

The orphan nuclear pathway (regulated by pyrimidine TAT and TAC kinases and OPA1 enzymes) has the roles of producing gamma-subunits, Beta-subunit, and alpha-subunits (fatty Acyl-COA-beta) upon the effects of synthetase, synthase, and phospholipase on fatty Acyl-COA (pro-inflammatory molecules) respectively (which produced upon effects of Cox2 and ATPase on inflammation molecules), that beta subunits are the basic tools for Glucocorticoids-beta synthesis which promote both mineralocorticoid and B-arrestin Biosynthesis, where B-arristin (via B Adrenergic and via nrf2 production) adopt ACE functions for Ang2-AT2 synthesis from Ang1-AT1 (that Ang1-AT1 ratio will be adopted in blood) then followed by VEGF-A productions which necessary for anti-inflammatory growth and heme oxygenase (regulated by Nrf2).

The Inhibition in OPA1 repairs (regulated by GTPase) and in pyrimidines kinases will reflect inhibition in Acyl-COA-gamma, and Acyl-COA-beta synthesis with inhibition in NR4As productive pathway which followed by cholesterol and long fatty chains (as pro-inflammatory molecules) accumulations with high affinity of binding with k and Na salts (that can cause lipotoxicity and diabetes) that will precipitate on blood vessels and can cause mutations in pro-inflammation, and also can cause accumulation in Interleukin-2 and in IL6 that can be improved For producing IL30 and IL40.

Estrogen synthesis depends on cholesterol productions regulated by OPA1 synthase function, that are so important steps for Acyl-COA-beta productions which activate glucocorticoid-beta synthesis . The mTOR pathway are reflecting the importance of the proper Ser /Thr phosphorylation pathway regulated by Cox2 and ATPase function for producing S6K, and the both kinases purines , for mTORC1 production, and for cholesterol productions which will be followed by proper OPA1 regulative functions for producing gamma, beta and alpha for cellular productive functions . The both purines and pyrimidines (regulating by synthetase) kinases are necessary for hydrophobic amino acids synthesis (which regulated by Proline productive functions) such as Leu, Glu, Tph, Ser, Thr, Tyr for running orphan nuclear pathway which controlled by proper OPA1 regulative functions .

The B-cells are known to be activated by Nrf2 and GCs-beta regulative functions that their functional activities depend on estrogen synthesis which depend on the estradiol synthesis which activate Glucocorticoids (GCs) synthesis in its three active followed forms started by gcs-gamma followed by GCs-beta then followed by GCs-alpha respectively, that GCs-beta synthesis will be followed by IFN-beta productions and will be mediated by B-arrestins productions which considered as adaptor active protein necessary for adopting several immune processes including stimulating ACE functions for activating and adopting Ang2-AT2 productions and activating VEGF-A synthesis necessary for anti-inflammatory growth and processes.

The deficiency In Aromatase can reflect diabetes and can be the result of osteoporosis, and Psoriatic arthritis (PsA) that can positively reflect reduction in GCs-beta and mineralocorticoid synthesis followed by reduction in IFN-beta productions and in both B-arrestins and in Nrf2 production followed by decreasing or inhibition in both angiotensin2 and in VEGF-A synthesis then followed by reductions in anti-inflammatory growth pathways, that will cause atherosclerosis, cirrhosis , cardiovascular diseases and cancers.

Case Reports

1st/: Rare case of glioblastoma multiform located in posterior corpus callosum presenting with depressive symptoms and visual memory deficits (that in normal cases the melatonin productive functions prevente spatial deficits in brain and induces CREB signaling pathways associated with long-term memory).

2nd /: Coronary artery disease (CAD) obstructs the supply of blood to the heart muscle through the coronary arteries. Atherosclerosis is main cause of CAD that, The Nuclear factor E2 related factor 2 (Nrf2) is a basic leucine zipper transcription factor that is activated in response to inflammation for running antioxidant functions that will improve inflammation molecules through

producing Interleukin-2, which act on inflammation and produce Interleukin-6 "IL6" (by NR4As) that upon Beta oxidation will produce IL17 which activate GCs-beta synthesis followed by B-arrestins and both B Adrenergic and Nrf2 productions which activate ACE for Ang2-AT2 and VEGF-A synthesis via NR4As pathway for activating liver, brain and heart myocardial functions . The availability of Tph "TGG", glutamine, Tyr, and Leu are so important for activating full proper NR4As productive pathway.

Vascular diseases, particularly atherosclerosis, are undoubtedly the leading causes of disability and death in patients with diabetes mellitus. Diabetes mellitus significantly increases the risk of developing coronary, cerebrovascular, and peripheral arterial disease.

The pathophysiology of vascular disease in diabetes involves abnormalities in the endothelial, vascular smooth muscle cell, and platelet function. The metabolic abnormalities characterizing diabetes—such as hyperglycemia, increased cholesterol (with decreasing in OPA1 functions that a combined with pro-inflammatory cytokines), and insulin resistance—provoke molecular mechanisms that contribute to vascular dysfunction.

Diabetes due to inhibition in hydrophobic acids synthesis which regulated by Pro where basically depends on pyrimidines kinases synthesis regulated by OPA1 synthetase functions.. Also inhibition in one of the ser/Thr phosphorylation pathway (such as inhibition in Ser phosphorylation) can lead to decreasing in the necessary active protein kinases, decreasing in amino acids synthesis, decreasing in building the active promoters in genes configuration synthesis such as estrogen synthesis and that will be followed by decreasing in glucocorticoids-beta synthesis then decreasing in both Nrf2 and angiotensin synthesis which will be followed by decreasing VEGF-A synthesis that will lead to activation to NGF but will lead to inhibition in anti-inflammatory growth.

Those previous mechanisms can include decreasing in NO bioavailability, increasing in oxidative stress, sever disturbances of intracellular signal transduction and can lead to the mutations within active subunits and primary genes structures. The NR4As productive pathway will be declared as important pathways that are responsible for IL6 which will be improved to IL17 that will activate glucocorticoid-beta synthesis followed by B-adrenergic productions which will activate Nrf2 synthesis for activating ACE for Ang2-AT2 and VEGF-A synthesis for running adopted anti-inflammatory growth. The abnormalities due to inhibition in NR4As pathway (may due to inhibition in pyrimidine kinases and in OPA1 functions) contribute to the cellular events that cause several diseases including atherosclerosis, cirrhosis, and cancers that subsequently increase the risk of adverse cardiovascular events in patients such as ischemic stroke. Diabetes can determines the onset of stroke and influences its prognosis by several mechanisms. A better understanding of those diseases and their mechanisms by which the hyperglycemia and diabetes exert their harmful effect on the onset and prognosis of stroke that should be understanded clearly and treated carefully and early as possible.

3d case report: Adrenocortical Carcinoma (ACC), And pancreatic ductal adeno carcinoma (PDAC), that caused due decreasing in Tph, Gln, Leu, Pro Ser, Thr That decreasing in Tph, Gln and Leu (followed by inhibition in mitochondrial OPA1 functions and repairs) that will cause mutations in the composition and activities of those cells, that those amino acids are so necessary for reactivating glucocorticoids (starting by serotonin for activating melatonin production for activating glucocorticoids synthesis) synthesis for modulating antioxidative stress (mediated by B-arrestins, B-adrenergic and Nrf2 respectively), anti-inflammatory growth, heme oxygenase, heart and brain protections and activating immune survival.

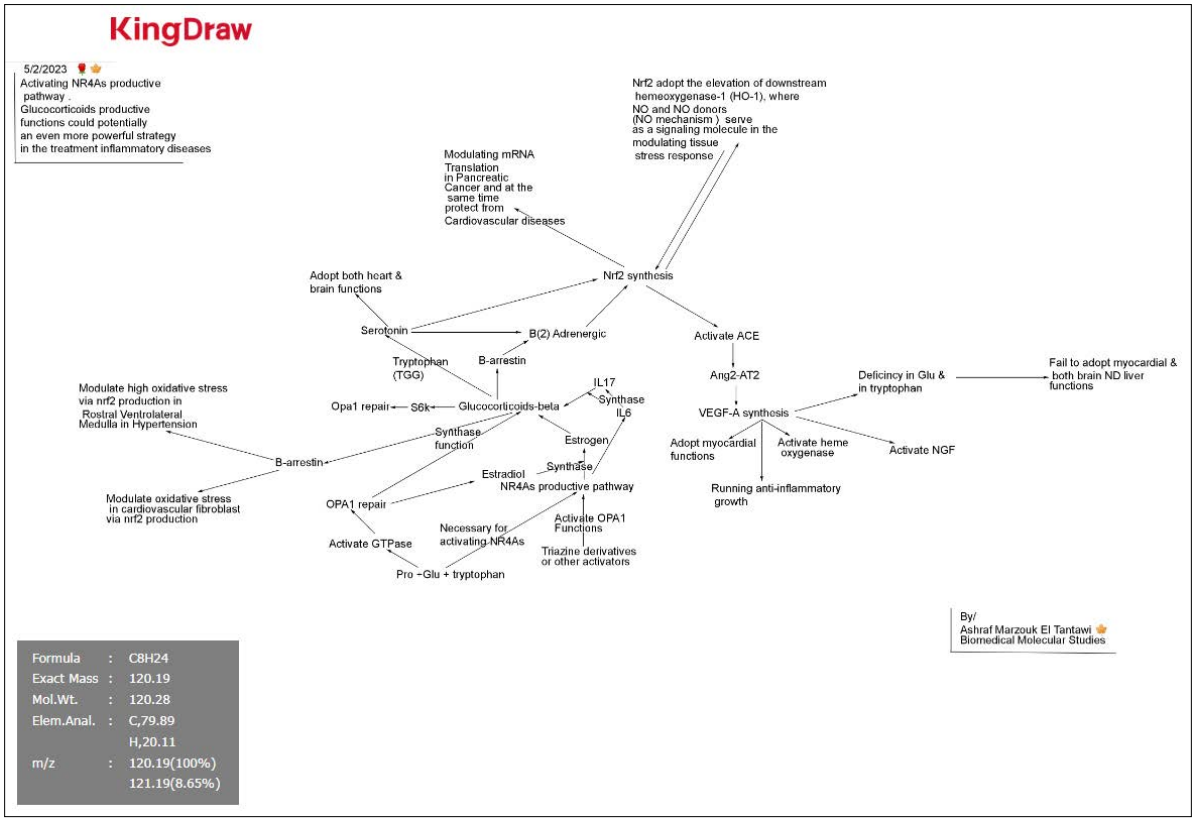

Figure 1

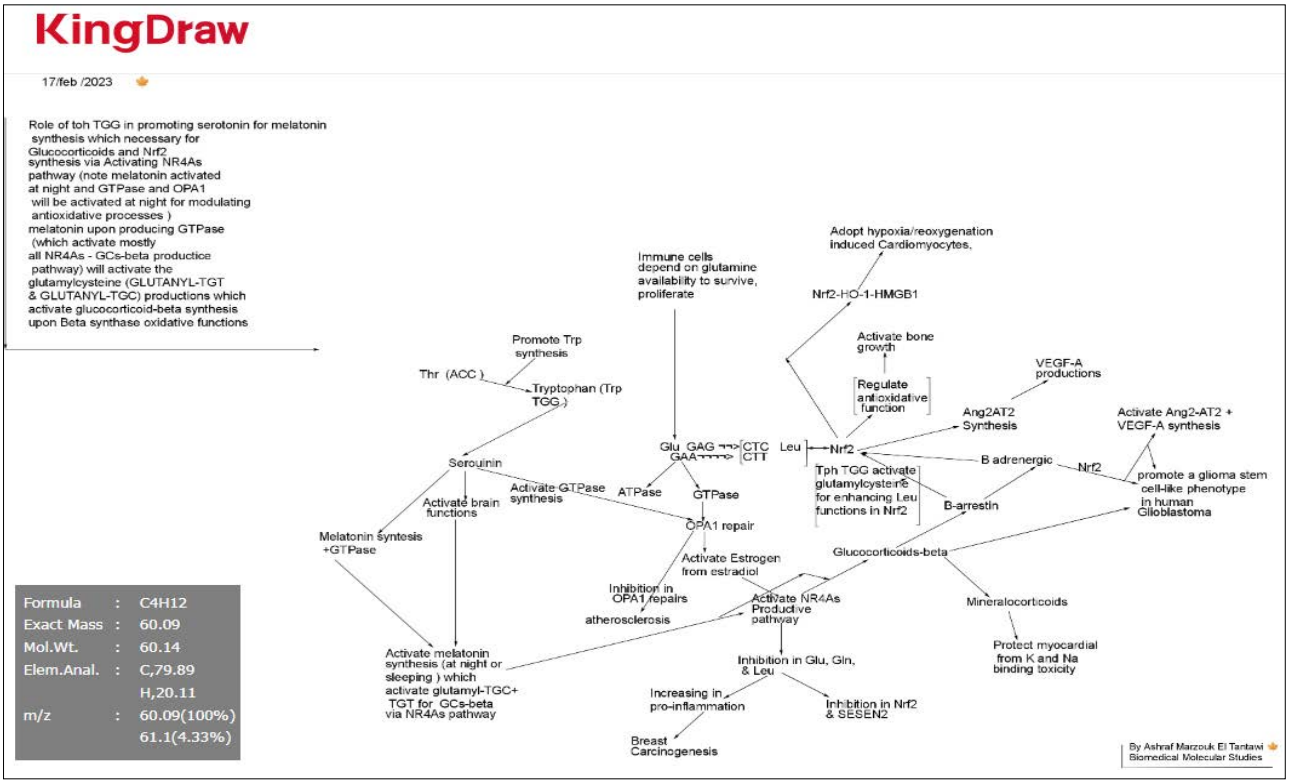

Figure 2

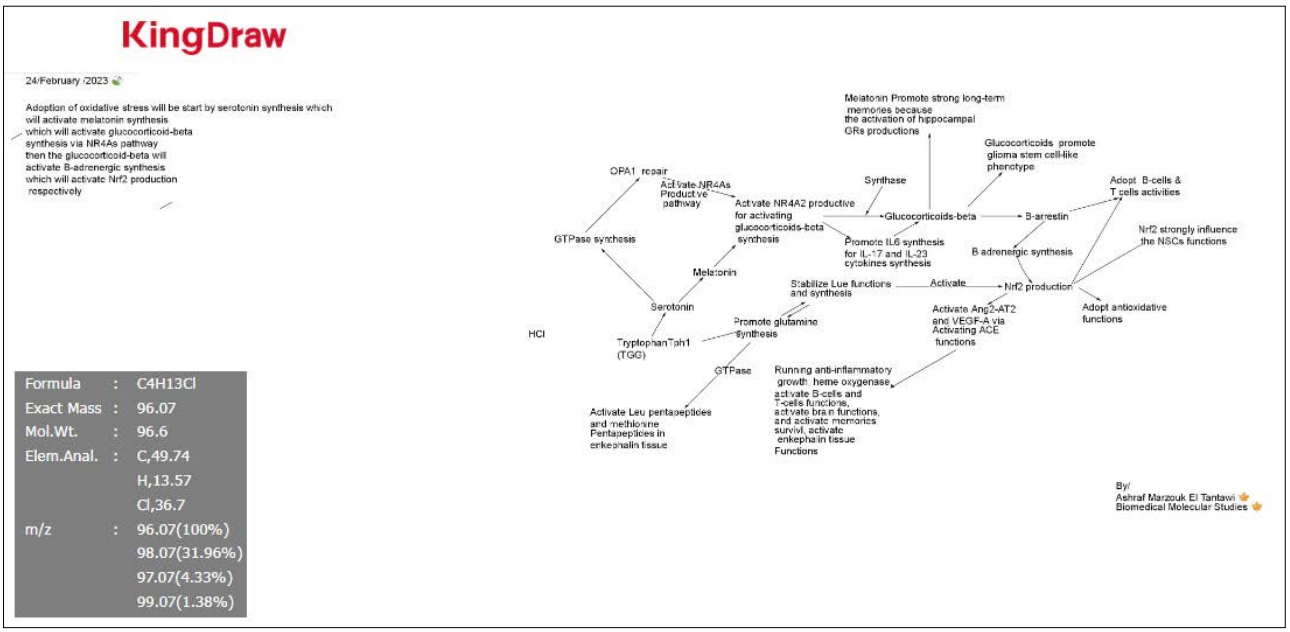

Figure 3

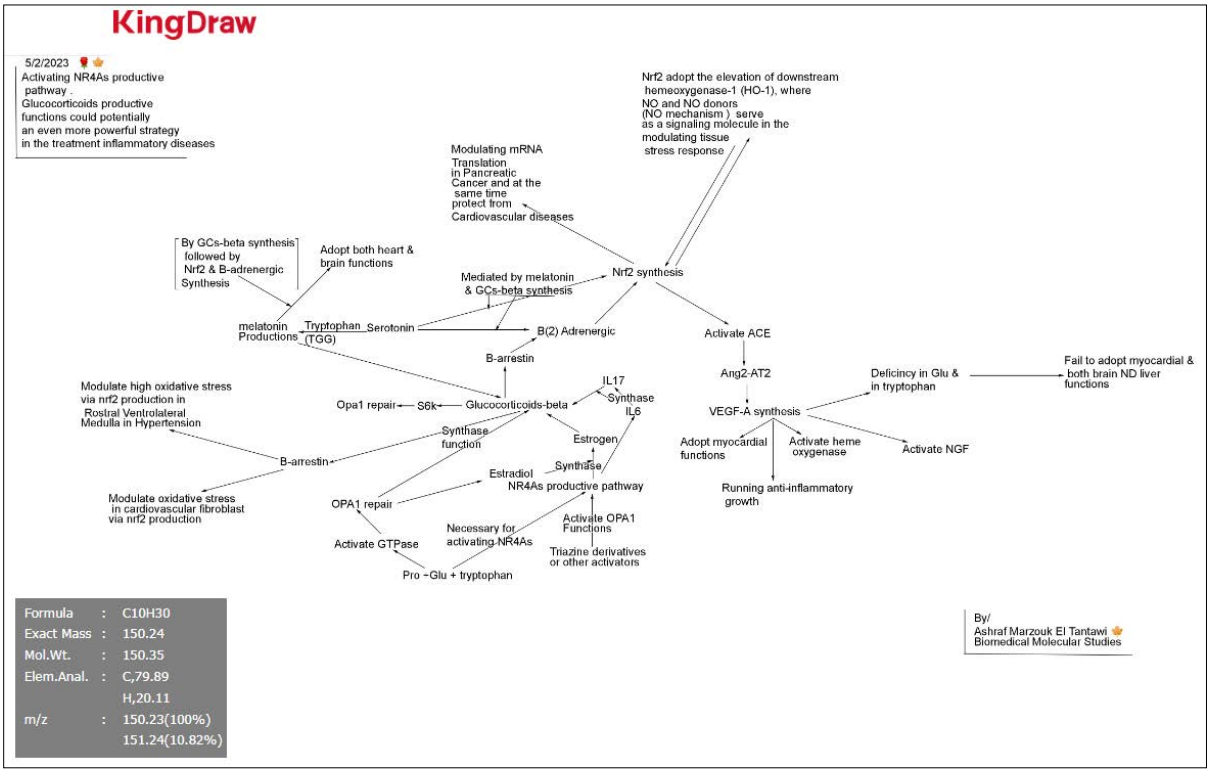

Figure 4

Methods and Results

Estrogen Biosynthesis are the functional productions that activate citrate synthase for deriving citrate-acetyl-CoA formation via RORs pathway through running lipogenesis , that deficiency in estrogen synthesis will reflect decreasing in lipogenesis pathway with accumulation in cholesterol and in pro-inflammation (which basically produced by Cox2 and ATPase functions), that the decreasing in estrogen will decrease or inhibit GCs-beta synthesis followed by reductions in both B-adrenergic and in Nrf2 7with increasing in GPCRs) that can lead to diabetes and cardiovascular disease, Hepatitis, cirrhosis, and decreasing in the activity of brain functions. That it has been reported that that synthase (CS) plays a critical role in providing citrate derived acetyl-CoA for lipogenesis and cholesterol genesis [1].

The production of the two purines and pyrimidine kinases by Ser/Thr phosphorylation are so imp for S6K productions and mTORC1 which are necessary for reactivating Akt/GSK3β/Fyn kinase axis The S6K necessary for regulating G-protein included GPCRs synthesis where the GPCRs ratio which necessary for GCs-beta and B-arrestins synthesis for producing both Ang2-AT2 and VEGF-A productions for anti-inflammatory growth and heme oxygenase.

That Deficiency in estrogen-GCs productive pathway will reflect Deficiency in B-arrestins and Nrf2 followed by decreasing in both angiotensin2 and heme oxygenase and followed by Deficiency in anti-inflammatory growth. The deficiency in estrogen-GCs-beta productive pathway (NR4As pathway) will be result of increasing in oxidative processes and accumulation in both pro-inflammation and cholesterol that lead to deficiency in angiotensin-2 (Ang2-AT2) and will lead to cardiovascular disease, Hepatitis, cirrhosis, and affect on activity of brain function. That deficiency in Ang2-AT2 synthesis leads to irritability and anger in the myocardial muscles cells that will reflect increasing in the GPCRs ratio with decreasing in GCs-beta and in mineralocorticoid synthesis which leads to increasing in k and Na binding toxicity in heart layers and in blood vessels.

Carcinogenesis characterized by chronic liver inflammation and regeneration processes with decreasing or inhibition in both GCs-beta and in Nrf2 synthesis which ultimately lead to oncogenic mutations in many cellular signaling cascades that drive cell growth by activating NGF and proliferation (with inhibition in anti-inflammatory growth).

Inhibition in OPA1 synthetase will lead to inhibition in pyrimidine synthesis and inhibition in pyrimidine kinases followed by inhibition in estrogen synthesis, also the inhibition in Proline synthesis and in hydrophobic amino acids synthesis can will ensure inhibition in estrogen productive pathway , and will cause increasing in Cox2 oxidative functions with increasing in the inflammations with accumulation in cholesterol.

The Inhibition in synthase (due to inhibition in pyrimidine synthesis) that will cause reductions in the full NR4As productive pathway (we'll discuss and declare later the full NR4As productive functional pathway) with reduction in GCs-beta synthesis and in Nrf2 productive functions that will cause inhibition in the adopted anti-inflammatory growth pathway with increasing in both 1stly /increasing in the oxidative process with increasing in mutated amino acids, 2ndly /inhibitiontin anti-inflammatory growth that can be the result of causing diabetes, cancer, Cirrhosis, and cardiovascular diseases.

The nuclear receptors "NR4As" productive pathway is one of the important pathways for the Manipulation of the classic ligand-activated nuclear receptors, and estrogen receptors productions which are important for regulating the adopted cellular anti-inflammatory growth mediated by GCs-beta productions which is the basic for activating B-arrestins synthesis which activate Nrf2 synthesis, that Nrf2 has the roles of activating ACE functions

for activating Ang2-AT2 and VEGF-A synthesis for running the adopted anti-inflammatory growth. Orphan nuclear receptors, such as nuclear family 4 subgroup A (NR4A) receptors are recognized as the primary molecular switches for cell survival, protection, and a molecular link between inflammation and genes Biosynthesis (GCs-beta, B-arrestins, Nrf2, angiotensin and VEGF-A synthesis) basically regulated by the proper mitochondrial OPA1 membrane functions.

NR4As has important role in modulating and improving oxidative stress and processes. That the function of NR4A1 is implicated in various metabolic processes, including carbohydrate, metabolism, lipid metabolism, adopting energy and anti-inflammation, in major metabolic cellular processes, such as liver, brain and skeletal muscle. That the NRs and exercise-induced muscle remodeling [2]. The Nur77 seems to be a promising target in future HF, that several nuclear receptors and hormone receptors, including the mineralocorticoid receptor and estrogen receptor, are well-known to modulate cardiac disease [3].

That, the NR4As productive pathway adopt and modulate fatty acids Oxidative Pathways that describe the mechanism of antioxidant by regulated by orphan nuclear functional pathways (upon proper OPA1 regulations) for activating B oxidations which activate both fatty Acyl-COA-beta and activate GCs-beta that necessary for B-arrestins and Nrf2 synthesis which adopt Ang2-AT2 followed by VEGF-A productive functions.

That, the Liver-specific Loss of Long Chain Acyl-CoA Synthetase-1 Decrease Triacylglycerol Synthesis and β-Oxidations and Alters Phospholipid Fatty Acid Composition [4]. The gamma oxidation which is activated by synthetase (upon its effect on pro-inflammatory molecules) for Acyl-COA-gamma production is the 1st adopted and improved step-in NR4As functional pathway followed by activating beta- oxidations for Estrogen and glucocorticoid-beta synthesis which are necessary modulate cardiac functions and for B-cells maturation and functions. That the Deficiency in the Acyl-COA-gamma synthesis will lead to increasing in accumulated cholesterol and in pro-inflammation with increasing oxidative processes followed by Deficiency in the adopted genes productions that will be result of Altering Phospholipid Fatty Acid Compositions. NR4As functional pathway are necessary for reducing inflammatory molecules that prevent the accumulation of inflammation and prevent mutations that are responsible for the effective genes productions (GCs-beta, B-arrestins, and Nrf2 synthesis) for activating anti-inflammatory growth mediated by Ang2-AT2 and VEGF-A synthesis.

That it has been reported that NR4A receptors act on inflammatory disease, and control the extent of inflammatory response [5]. The NR4As pathway are having the role of controlling the extent of the inflammatory response for activating Estrogen productions through activating Acyl-COA-beta for promoting GCs-beta, B-arrestins synthesis (where NR4As are nuclear resonance or β-arrestin2 biosensors) which followed by Nrf2 production which activate ACE functions for Ang2-AT2 synthesis followed by VEGF-A productions "respectively" for anti-inflammatory growth and processes. The NR4A nuclear receptors sub-family (Nur77, Nurr1 and NOR-1) are emerging as important key in cardiac stress responses and adoptions; Where Nur77 seems to be a promising target in HF characterization and Therapy [6]. And in the heart itself the Nur77 is emerging as a key player in adverse cardiac remodeling [7]. NR4As exert multilevel regulations of cardiac function and diseases as a primary modulator to pro-inflammatory molecules and mediator or stimulator to GCs-beta and both B-arrestins and Nrf2 that activate angiotensin when protect and adopt cardiac constrictions and functions.

That the Prolonged primary nuclear factor means dysfunction in some of followed activated steps for modulating pro-inflammation and GPCRs , that can be the result of causing mutation (due to accumulation) in pro-inflammation which will stimulate Tumor growth factor and will cause un-adopted growth which can lead to dilated cardiomyopathy. Where it is reported that Prolonged cardiac NR4A2 activation causes dilated cardiomyopathy in mice [8].

It's clear that NR4As functional pathway has strong roles of the primary adoption to the oxidative processes and improve the antioxidative progressive pathway, that NR4As is the main for Acyl-COA-gamma followed by Acyl-COA-beta synthesis (regulated by synthase) which promote GCs-beta synthesis followed by IFN-beta and B-arrestins synthesis then followed by Nrf2 production which stimulate ACE functions for Ang2-AT2 synthesis and VEGF-A necessary for anti-inflammatory growth, where inhibition in one or more of mediator steps in NR4As pathway will cause disease progression.

That dysregulation of NR4As affects cytokine productions by cDC2s and modulates downstream T cell [9]. Previous study indicated that the NR4As productive pathway has the role of acting on pro-inflammatory for producing IL6 which will be improved to IL17 production by synthase function for activating Acyl-COA-beta which promote GCs-beta and Estrogen synthesis which has the roles of modulating T cell functions and cell survival, where dysfunction in NR4As pathway are characterized by inflammatory diseases, cardiovascular diseases, and cancers.

The precursor-like" MZ B-cells have been characterized by NR4As expression that associate with regulatory potential of T-cell regulatory (Treg), that dys-regulation in NR4As pathway will cause downstream in T-cells and indicating the evolving of NR4As in activating anti-inflammatory responses pathways. That it has been reported that mature MZ and precursor-like MZ B-cells express nuclear receptors NR4A1, 2, and 3, known to be associated with T-cell regulatory (Treg) maintenance and function [10].

The transcription factors Nuclear Receptors (NR) 4A1, NR4A2 and NR4A3 are heavily involved in anti-inflammatory responses, that the Deficiency in NR4As pathway will be result of increasing in inflammatory and pro-inflammatory molecules . That It has been reported that "the loss of NR4A2 expression" leads to enhanced NF-κB activity and hyper inflammatory responses in myeloid cells [11]. So it's clear the involvement of NR4As in anti-inflammatory pathways started by acting on inflammation and improvements to the DC functions for activating estradiol and estrogen synthesis via Acyl-COA-beta productions by synthase function for activating GCs-beta and B-arrestins followed by Nrf2 activation which activate ACE functions for producing Ang2-AT2 followed by VEGF-A synthesis. That the MZ B-cells which characterized by NR4As expression possess a strong B-cell regulatory (Breg) function [12]. So NR4As active pathway possess controls and adopt the oxidative functions and has the role of regulating Breg and T-cells functions.

The β2-Adrenergic receptor (β2-AR) produced by NR4As pathway for regulating Nrf2 synthesis mediated by GCs-beta and B-arrestins

The β3-adrenergic receptors is selectively expressed in brown adipose tissue present in rodents and in newborn humans, that

the β3-adrenergic receptors has important roles in preventing myocardial fibrosis by modulating antioxidative function. The β3-adrenergic responsible for lipolysis, thermogenesis, adopt muscle relaxation and have demonstrated as ant-istress in animal studies. Beta-adrenergic receptors, including the β1, β2, and β3-adrenergic receptors, are a component of the adrenergic nervous system. The β-arrestin 1 regulates β2-adrenergic receptor-mediated skeletal muscle hypertrophy and contractility. That unappreciated role for β-arrestin 1 in mediating β2AR-stimulated skeletal muscle growth and strength [13].

And β3-adrenergic receptors activations may attenuate elevated vasoconstriction observed in Hypertension [14]. So β3-adrenergic receptors can improve and adopt vasoconstriction through activating Ang2-AT2 synthesis and can adopt oxidative processes through activating Nrf2 production followed by both Ang2-AT2 and VEGF-A synthesis that will adopt GPCRs ratio in blood.

Also, β3-adrenergic receptors adopt and improve arterial tone started by adopting the myocardial constrictions which known to be adopted by Ang2-AT2 productive functions (regulated by B-arrestins) whichh adopt the GPCRs ratio in blood [15]. So we considere that B-arrestins regulate β2-adrenergic receptors productive functions (mediated by GCsbeta synthesis).
Which involved in regulating and promoting Nrf2 productive functions too then followed by activating Ang2-AT2 and VEGF-A synthesis for adopting anti-inflammatory growth which included heme oxygenase and antioxidative adoption. Also GCs-beta adopt and regulate B-cells maturation necessary for stem cells (mesenchymal stem cells "MSCs Renewal) and necessary for protecting myocardial functions)} protect neurons from death by trophic factor withdrawal or nitric oxide (NO) exposure [16].

GCs-beta productive functions is the main regulations for regulating MSc for protecting neurons from death by trophic factor withdrawal or nitric oxide (NO) exposure which mediated and regulated by β2-adrenergic receptor- B-AR productions. That, Endothelial β3-Adrenoreceptors Mediate Nitric Oxide–Dependent Vasorelaxation of Coronary Microvessels [17]. So we can concluded that glucocorticoids productions regulate B-arrestins synthesis which regulate β3-adrenergic receptors synthesis which the attenuation of the elevated vasoconstriction and having also the role of adopting muscle. Hypertrophy and contractility and also regulates the skeletal muscle growth and strength through activating anti-inflammatory growth mediated by activating both Ang2AT2 and VEGF-A synthesis which basically activated by B-arrestins which adopt the stimulation of ACE functions. And, Cardiac myocyte β3-adrenergic receptors prevent myocardial fibrosis by modulating oxidant [18]. And, β2-Adrenergic receptor B2-AR inhibition inhibit Nrf2 productive functions. That it has been indicated β2-AR inhibition induces oxidative stress blocking NRF2 nuclear translocation [19].

So in brief we concluded that B-arrestins regulate B-Adrenergic receptor which positivity regulate Nrf2 synthesis (in the NR4As pathway). And also, Beta-1-adrenergic receptors mediate Nrf2-HO-1-HMGB1 axis regulation to attenuate hypoxia/reoxygenation-induced cardiomyocytes injury in vitro [20]. So it's clear that Beta-1-adrenergic receptors (which regulated by B-arrestins) regulate Nrf2-HO-1-HMGB1 axis regulation to attenuate hypoxia/reoxygenation. Note the attenuation of hypoxia/reoxygenation-induced Cardiomyocytes by Nrf2 means having the role of adopting myocardial constrictions and having the role of activating angiotensin and VEGF-A synthesis for anti-inflammatory growth. And also, Selective activation of adrenergic β1 receptors induces heme oxygenase 1 production in RAW264.7 cells [21].

So, strongly we can concluded that: B-arrestins regulate B Adrenergic productions which regulate Nrf2 synthesis and functions which necessary for activating both Ang2-AT2 and VEGF-A "respectively" for activating the adopted anti-inflammatory growth, adopt vasoconstriction, and induces heme oxygenase 1 production in RAW264.7 cells.

That B-adrenergic synthesis are so necessary to be involved for modulating all antioxidative stress in all tissues for running anti-inflammatory growth, that in cases of inhibition in B-adrenergic will cause inhibition in antioxidative stress that will inhibit skeletal muscle growth, inhibit the progress of the of vasoconstriction and also will cause mutations in cellular composition and functions.

And strongly we can concluded that NR4As pathway activate GCs-beta synthesis which regulate B-arrestins which is adopter active protein that control and regulate β2-adrenergic productive function which regulate Nrf2 productions (where inhibition in β2-adrenergic will inhibit Nrf2 antioxidant productive functions), then followed by preventing myocardial fibrosis by modulating oxidant, then promoting Nrf2-HO-1-HMGB1 axis regulation (mediated by β2-Adrenergic) to attenuate hypoxia/reoxygenation-induced Cardiomyocytes, and then adopting heme oxygenase mediated by activation of Ang2-AT2 and VEGF-A synthesis by Nrf2 functional activities.

And more the Beta (2)-adrenergic receptors synthesis involved in the NR4As productive pathway and firstly potentiated and regulated by both GCs-beta and B-arrestins. That it has been reported that through feedback the Beta (2)-adrenergic receptors can potentiate glucocorticoid receptor transactivation via G protein, beta-subunits synthesis, and the phosphoinositide 3-kinase pathway [22].

Also, as B-Adrenergic produced as directly will activate Nrf2 followed by Ang2-AT2 and VEGF-A synthesis respectively , where the Angiotensin productive roles are included adopting myocardial constriction, where Ang2-AT2 through feedback can activate B-Adrenergic followed by B-arrestins and GCs-beta productions. That it has been indicated that Ang II α1a-AR mediated expression of the immediate-early gene c-fos in cardiac myocytes [23].

So in conclusion the main NR4As productive pathway is NR4As¬>GCs-beta ¬>B-arrestins ¬>B-Adrenergic ¬>Nrf2 ¬>activate ACE ¬>Ang2-AT2 and VEGF-A synthesis ¬>heme oxygenase¬>adopting myocardial constrictions¬> adopt vasoconstriction ¬>activate anti-inflammatory growth.

NR4As productive pathway necessary for GCs-beta and B-arrestins, followed by B-adrenergic receptors, and Nrf2 for angiotensin-2 synthesis respectively

NR4A2 is an active mediator for acting on inflammatory sources for begin adopting the antioxidative processes (and thermal adoption) via augment the activities of IL-17 and IFN-γ genes productions which then will follow the effects of synthase function for GCs-beta and IFN-beta productions. That it reported that the expression of NR4A2 augmented promoter activities of IL-17 and IFN-γ genes, leading to an excessive production [24]. As mentioned early that NR4As has the role of improving the DCs-2 productive functions (for producing IL6 followed by IL-17 productions) upon OPA1 synthase function for activating Acyl-COA-beta which necessary for GCs synthesis. Where it has been

reported that IL-17 and IL-23 cytokines significantly increase GR-beta expression. That GR-beta up-regulation by IL-17/IL-23 cytokines is associated with induced steroid insensitivity in PBMCs [25].

So, it's clear that NR4A2 has the roles of acting on pro-inflammatory molecules for modulating DCs-interleukin 2 activities for producing IL17 which necessary for regulating GCs-beta synthesis (upon OPA1 synthase function) followed by B-arrestins synthesis and then Beta (2)-adrenergic production which modulate antioxidative stress and activate Nrf2 production for adopting antioxidative functions and for activating heme oxygenase mediated by Ang2-AT2 and VEGF-A synthesis for anti-inflammatory growth respectively.

Notice, NR4As promote firstly GCs-gamma followed by GCs-beta productions which will activate IFN-beta productions in one branched pathway but the other main pathway will be for activating B-arrestins followed by B Adrenergic for activating Nrf2 production "respectivily" for both Ang2-AT2 and VEGF-A synthesis. Where, glucocorticoids are having the basic roles for activating and adopting IFN functional production and promoting B-arristin for adopting Ang2-AT2 and VEGF-A productive functions [26].

Also, glucocorticoids (which regulated by NR4As pathway) impair upstream B cell receptor ((mediated by B-adrenergic functions)) and Toll-like receptor 7 signaling, reduce transcriptional output from the three immunoglobulin loci, and promote significant up-regulation of the genes [27].

So, So, the GCs-beta synthesis linked to cell type–dependent transcriptional responses that activate NR4As pathway for glucocorticoids synthesis for upregulate B-cell and promote up-regulation of the genes and heme oxygenase via B-arrestins and both B-adrenergic and Nrf2 productions respectively followed by both Ang2-AT2 and VEGF-A productions for running the full adopted anti-inflammatory growth.

And it has been reported that: The Murine Glucocorticoid Receptors Orchestrate B-cell Migration Selectively between Bone Marrow and Blood, and mature B cells in bone marrow are capable of responding to blood-borne [28].

Means, Murine Glucocorticoid Receptors adopt (Orchestrate) B-cell Migration Selectively between Bone Marrow and Blood, and mature B cells in bone, where migration between bone marrow and blood via Activating NR4A2 pathway For regulating heme oxygenase and anti-inflammatory growth (which activated by Nrf2), and adopt "control" the mature B-cell which mediated by the adopter protein B-arrestins and Nrf2 for activating Ang2-AT2 and VEGF-A for adopted growth by anti-inflammatory growth and processes. The Increasing in stress will stimulate serotonin synthesis upon the availability of Tph "TGG" (where both serotonin and melatonin are activating memories and brain functions) which will activate melatonin synthesis the has the role of activating. Glucocorticoids receptors "GRs" synthesis via NR4As pathway that will activate B-arrestins synthesis followed by both Beta-adrenergic and Nrf2 productions which adopt the antioxidative functions followed by Ang2-AT2 and VEGF-A synthesis for heme oxygenase, for activating glioma stem cell-like phenotype and for running full anti-inflammatory growth including brain memories growth. Where it has been reported that the increasing in stress will promotes the formation of strong long-term memories because the activation of hippocampal GRs productions [29].

that increasing in stress will activate melatonin synthesis from seratonin (regulated by Tph TGG) that will activate glutamine synthesis for Leu synthesis that will activate both B-adrenergic (which reported early that produced in bone marrow) and Nrf2 functions that will modulate antioxidative stress and both bone and brain functions including modulating T-cells functions and Recirculating B cells localize to perivascular spaces in bone marrow populated with T cells and dendritic cells. And, the Recirculating B cells will be via Activating NR4As productive pathway for reactivating GCs-beta which promote B-arrestins for regulating both Beta(2)-adrenergic followed by Nrf2 production for activating both Ang2-AT2 and VEGF-A for heme oxygenase and for anti-inflammatory growth including activating T cells which localize to perivascular spaces in bone marrow populated with T-cells. That has been reported Recirculating B cells localize to perivascular spaces in bone marrow populated with T cells and dendritic cells [30]. Also it has been indicated Glucocorticoids promote a glioma stem cell-like phenotype in human Glioblastoma [31].

So via Activating NR4As productive pathway the GCs-beta will be activated for promoting glioma stem cell-like phenotype and for activating antioxidative function via Activating Beta (2)-adrenergic for regulating Nrf2 productions followed by activating angiotensin and VEGF-A synthesis which are necessary for anti-inflammatory growth and for heme oxygenase respectively.

And So it's clear that stress stimulate firstly the serotonin productions which activate melatonin (upon the stimilatted stress) which will activate glucocorticoid-beta Via nuclear NR4As productive pathway followed by activating B-arrestins and Nrf2 synthesis (mediated by Beta (2)-adrenergic synthesis) respectively for adopting the activation of Ang2-AT2 followed by adopting the activation of glioma stem cell-like phenotype in human Glioblastoma through activating anti-inflammatory processes (notice, it has been considered that Nrf2 having strong roles in activating the adoption the basic function of stem cells).

That Despite GCs promote stem cells functions, the NRF2-dependent regulation of redox homeostasis plays a critical role in mediating the ability of different stem cell types to differentiate or survive oxidative insult, and the NRF2's role in regulating the stress response can now be revised to include the basic function of stem cells [32].

So, GCs promote stem cells functions via Nrf2-dependent regulation of redox homeostasis by mediating the ability of different stem cell types to differentiate or survive oxidative insult. And also both B-adrenergic (which located in bone marrow that modulate bone growth) and Nrf2 which located in bone marrow too are having the roles of modifying and modulating antioxidative stress for adopting bone growth and adopt NSC survival and neurogenesis.

That it has been reported that: And also Nrf2 can strongly influence the NSCs function (adopt NSCs productive functions) and fate determination by reducing levels of reactive oxygen species in benefit of NSC survival and neurogenesis [33].

So it's clear that Recirculating B cells (and modulating antioxidative stress will be done by activating melatonin synthesis by serotonin for activating glucocorticoids synthesis via NR4As pathway) will be done through activating NR4As productive pathway for activating glucocorticoid-beta For activating anti-inflammatory processes mediated by B-arristin synthesis which activate Beta(2)-

adrenergic production for activating Nrf2 production for activating "respectively" Ang2-AT2 and VEGF-A synthesis for running anti-inflammatory growth and for adopt NSC survival and neurogenesis including bone growth [34].

Note that Transfection is a procedure that introduces foreign nucleic acids into eukaryotic cells, Transfection of Sponge Cells occur due to increasing in oxidative damage with reduction in both B-adrenergic and in Nrf2 productive function that Nrf2 has the roles of activating adopted bone growth and T-cells modulated functions. I would like to note that : only the direct activating of Nrf2 from the middle of NR4As pathway will be directly helpful for adopt heart rhythm and adopt GPCRs and Ang1-AT1 ratio through adopting both Ang2-AT2 and VEGF-A synthesis, while starting by activating GCs-beta via activating NR4As pathway will start to be helpful for activating the regulation of mineralocorticoid productions which necessary for protecting heart layers from K and Na binding toxicity then will be followed by regulate both B-arrestins and Nrf2 productions for protecting and adopting heart constrictions (mediated by Ang2-AT2 and VEGF-A synthesis) and function that will protect from cardiovascular disease .

How Regulation of mitochondrial oxidative functions done by glucocorticoids, by B-arrestins in cardiovascular fibroblast and by Nrf2 functions?: Firstly, it's already considered that atherosclerosis can be exacerbated by high unadopted oxidative stress. The unadopted oxidative stress will reflect decreasing or inhibition in serotonin and consequently inhibition in melatonin (which necessary for activating glucocorticoids "GCs" synthesis via NR4As) that will reflect Inhibition in the stimulation of NR4As (which stimulated by melatonin in the case of modulating high stress for activating GCs-beta synthesis) that will lead to accumulation in IL2 and IL6 (with inhibition in IL17) that will lead to increasing in the accumulated Low density lipoprotein "cholesterol" (with inhibition in estrogen). The Deficiency In activating NR4A2 by melatonin will lead to decreasing in estrogen and in GCs-beta synthesis then will lead to accumulation in cholesterol that oxidative processes will increased for more pro-inflammatory which is the main for atherogenesis.

The sever Deficiency In NR4As productive pathway can be the main reasons for causing atherogenesis, autoimmune disorders, and cardiovascular diseases.

That, the production of Glucocorticoid Receptor via NR4As Modulates the reactivating the Autoregulation of Ribosomal Protein S6-Kinase which are indispensable by DNA binding and transcriptional activation that the modulation and activation of S6K are necessary for ribosomes repairs and for both ATPase and GTPase productions, that GTPase are so necessary for medulating OPA1 membrane repairs (that GTPase produced by Tph TGG functions due to serotonin and melatonin synthesis), where the reactivating OPA1 functions are necessary for modulating the adoption of oxidative processes where upon OPA1 the estrogen will be produced and will activate GCs synthesis and the DCs Interleukin-2 will be improved for IL6 and IL17 production which necessary for GCs which synthesis then followed by B-arrestins, B Adrenergic, and Nrf2 productions respectively that will activate ACE for Ang2-AT2 and VEGF-A synthesis which has the roles of adopting myocardial constrictions, protecting heart function, adopt GPCRs ratio in blood, activating heme oxygenase (regulated firstly by mediated Nrf2 functions), and activate the anti-inflammatory growth.

It has been reported that: The Activated Glucocorticoid Receptor Modulates Presumptive Autoregulation of Ribosomal Protein S6 Protein Kinase, p70 S6K [35]. That the tryptophan (Tph TGG) amino acids which activate serotonin and melatonin synthesis for reactivating glucocorticoids synthesis are having the rules of activating GTPase synthesis which activate S6-Protein kinases and activate OPA1 repairs for activating orphan nuclear pathway .

Actually not only glucocorticoid Receptor Modulates Presumptive Autoregulation of Ribosomal Protein but also Nrf2 are having the role of activating protein kinase synthesis through reactivating Glu synthesis from Leu upon translations process where Leu is the main active amino acids for Nrf2 functional activities.

The Modulation Presumptive Autoregulation of NR4As and OPA1 function can begin by Tph TGG (which necessary for activating serotonin followed by melatonin "due to the percentage of stress") will reactivate glutamine synthesis which connected to Leu synthesis and stability for stabilizing Nrf2 functions for modulating antioxidative function. Where regulating the oxidative processes and hypertension will be done firstly by Tph TGG functions for activating both serotonin and melatonin for activating glucocorticoids synthesis via NR4As pathway and also with the done by modulating mitochondrial OPA1 functional activities (that OPA1 repair regulated by GTPase) functions which modulate glucocorticoids productive functions via NR4As pathway. B-arrestins (which regulated by GCs-beta) play important roles in adopting oxidative stress and adopt mitochondrial oxidative stress in cardiovascular fibroblast via regulating Nrf2 productions, that It has been reported that : β-Arrestin1 Reduces Oxidative Stress (adopt oxidative processes) via Nrf2 Activation in the Rostral Ventrolateral Medulla in Hypertension [36].

And it has been revealed that: The Regulation of mitochondrial oxidative stress by B-arrestins in cardiovascular fibroblast [37]. That the same mechanism that mentioned previously of tryptophan function for modulating antioxidative stress can be done in cardiovascular fibroblast by B-arrestins and will be done in bone marrow during activating stem cells functions and bone growth mediated by both B-adrenergic and Nrf2 productive functions too. Also the NR superfamily, the NR modulator NR-NR crosstalk, dual NR/alternative targets modulators could potentially become an even more powerful strategy In the treatment of inflammatory diseases . [38].

That as glucocorticoid receptors (GR/NR3C1) are having the the roles of regulating both B-arrestins and Nrf2 synthesis as all of them (via NR4As productive pathway) are having the powerful strategy In the treatment inflammatory diseases.

And the Regulation of oxidative stress can started firstly by serotonin followed by melatonin synthesis for activating NR4A2 pathway for GCs-beta synthesis which will regulate B-arrestins synthesis for promoting firstly Beta(2)-adrenergic followed by Nrf2 productions which will modulate the oxidative stress And will activate Ang2-AT2 and VEGF-A synthesis (by activating ACE functions) for activating anti-inflammatory growth. That, NR4A1 promotes oxidative stresses after myocardial ischemia reperfusion injury [39]. And, NR4As may promote (modulate) glucose utilization in muscles, adipose tissue, and islets, while NR4A1 may also promote glucose production in liver [40]. And, It has been reported that NR4As have significant regulatory effects on energy homeostasis and diabetes [41].

So, NR4A1 promotes oxidative stresses where oxidative stress can be due to fear or pathogenic oxidative stress or other that NR4As pathway will be stimulated by melatonin functional productions for

activating GCs-beta for activating Nrf2 for adopting antioxidative functions and running anti-inflammatory growth.

And again: the Regulation of oxidative stress can started firstly through activating serotonin followed by melatonin (regulated by Tph TGG) for stimulating NR4As pathway for re-activating GCs-beta productions which will regulate B-arrestins synthesis for promoting firstly Beta (2)-adrenergic followed by Nrf2 productions for adopting oxidative stress which protect heart function and activate brain memories and increase brain functions with protections to liver function.

Notice that protein kinases synthesis can be done through glutamine amino acid functions that through its degradation can activate purines and pyrimidine kinases then followed by Proline functions for amino acids synthesis including Leu synthesis for Nrf2 functions , and also more protein expression can be done by activating anti-inflammatory growth (activated by VEGF-A synthesis).

So in conclusion: Tryptophan "TGG" are necessary for activating serotonin which activate melatonin ¬>that will activate glucocorticoid-beta synthesis via NR4As ¬> where NR4As will promote estrogen from 17β-estradiol-mediated GPR30 activation ¬>then will activate GCs-beta¬> B-arrestins¬> B (2) -Adrenergic¬>Nrf2 ¬> Ang2-AT2 ¬> VEGF-A ¬> anti-inflammatory growth ¬>heme oxygenase ¬¬>adopt antioxidative functions ¬¬>adopté T-cells functions… etc.

Nrf2 functions regulated by NR4As productive pathway for activating antioxidative processes, Ang2-AT2 and VEGF-A production

Retinoic Acid Receptor-Related Orphan Receptors α (ROR beta) plays important functions for improving Nrf2 functional pathways but in availability of glutamine amino acids which necessary for leucine (which important for Nrf2 synthesis) started by NR4As and followed by GCs-beta synthesis and then continuing for B-arrestins and Nrf2 production followed by both Ang2-AT2 and VEGF-A productions for heme oxygenase and anti-inflammatory growth that basically depend on both purines and pyrimidine kinases synthesis.

That, glutamine can activate leucine synthesis upon translation and leucine can activate Glutamate formation via the leucine-to-glutamate pathway of rat pancreas [42]. Previously I clarified that NR4As productive functional pathway are the basic for regulating GCs-beta then IFN-beta, followed by B-arrestins and Beta(2)-adrenergic (regulated by tryptophan) which activate Nrf2 (regulated by Glu for Leu synthesis) synthesis then followed by activating ACE for both Ang2-AT2 and VEGF-A productions which necessary for running heme oxygenase and for both anti-inflammatory growth and processes.

It's Important to note that Loss of Nrf2 (due to inhibition in OPA1 synthase and in amino acids synthesis or due to deficiency in Glu amino acids) in some cases will reflect Deficiency in NR4As productive steps that can cause accumulation in IL2, IL6 and in pro-inflammation that will be the result to provokes Ang II-induced cardiac inflammation via IL-6/STAT3 signaling That it's reported the Loss of Nrf2 provokes Ang II-induced cardiac inflammation via IL-6/STAT3 signaling [43].

The loos of synthase (which has the role of improving IL6 for IL17 synthesis upon synthase function which activate GCs-beta synthesis) will be the main result of loosing GCs-beta productions with accumulation of cholesterol (due to inhibition in estrogen) followed by reduction in both B-arrestins and Nrf2 production that will be the result of the accumulation of inflammation in cardiac via IL-6 stat signaling with increasing in GPCRs ratio (due to inhibition in Ang2-AT2 and in VEGF-A synthesis) that will be the result of un adopted myocardial constrictions with increasing in K and Na binding toxicity (due to inhibition in mineralocorticoid synthesis) followed by increasing in left vertical size then will be associated with the progression of HF.

Also, NRF2 (promoted by Beta(2)-adrenergic in NR4As pathway) is considered as master transcription factor of antioxidant and thus is an attractive therapeutic target for cardiovascular diseases [44].

And, Nrf2 activators have a potentially beneficial role in improving autism-like behaviors and abnormal molecular alterations which caused by oxidant stress (that improving abnormal alterations will need activation to angiotensin & anti-inflammatory growth as indicated previously) [45].

That the activation the Nrf2 will activate directly ACE for activating both Ang2-AT2 and VEGF-A synthesis which will improve autism-like behaviors and abnormal molecular alterations through activating anti-inflammatory growth. Also, Nrf2/Wnt resilience orchestrates rejuvenation of glia-neuron dialogue (through activating anti-inflammatory growth mediated by Ang2-AT2 and VEGF-A synthesis that regulated by Nrf2 functions) in Parkinson's disease [46].

The rejuvenation of glia-neuron by Nrf2 (for activating the Nurr1 Pathway) can be done by either of two ways 1st first directly activate ACE for Ang2-AT2 and VEGF-A for anti-inflammatory growth, 2nd through translations that will activate Glu productions which it's degradations will activate purines and pyrimidine kinases (upon oxidative function) that will activate S6K synthesis followed by ATPase and GTPase production followed by mTORC1 synthesis and estradiol and amino acids synthesis that will activate the NR4As functional pathway from beginning for GCs-beta synthesis followed by mineralocorticoid synthesis and B-arrestins for protecting and adopting cellular functions followed by B Adrenergic synthesis (in availability of tryptophan) which adopt oxidative processes and activate Ang2-AT2 with VEGF-A for adopted growth and has the main roles for protecting and activating brain function and myocardial heart layers for proper constriction and protections, thet can be followed by an other sub-branched pathway which can reactivate Nrf2 for running antioxidative process and anti-inflammatory growth mediated by Ang2-AT2 and VEGF-A synthesis.

That Nrf2 rejuvenation of glia-neuron for activating the Nurr1 Pathway in Microglia and Astrocytes Protects Dopaminergic Neurons from Inflammation-Induced Death [47].

So Nrf2 can reactivate NR4As productive pathway Through rejuvenation of glia-neuron for activating the Nurr1 Pathway which will begin the NR4As productive pathway for protecting Dopaminergic Neurons from Inflammation-Induced Death. That as described before Nrf2 has strong functions for repairing and rejuvenation of glia-neuron re-function through activating Nurr1 for acting on pro-inflammation for regulating GCs-beta followed by both B-arrestins, followed by B-Adrenergic productions and then again B-Adrenergic will reactivate Nrf2 reproductions respectively which are so important pathway for protection from inflammatory diseases and for reactivating heart, brain, and immune survival.

That it has been reported: NRF2 Promotes Tumor Maintenance by modulating mRNA Translation in Pancreatic Cancer [48]. Also, the full NR4As productive pathway has the roles of Modulating mRNA Translation. In Pancreatic Cancer and at the same time protect from cardiovascular diseases. B-arrestins is the main regulator to Nrf2 (in the NR4As productive pathway) which can improve maintenance in pathogenic diseases and adopt directly the oxidative function mainly via Nrf2 productive functions. That it has been reported that: β-Arrestin1 Reduces Oxidative Stress via Nrf2 production [49]. Also, it has been proven that N-Acetyl Serotonin Alleviates Oxidative Damage by Activating Nuclear Factor Erythroid 2-Related Factor 2 Signaling [50]. So, via modulating oxidative stress the serotonin will activate melatonin which will activate glucocorticoid-beta synthesis which will promote B-arrestins for modulating antioxidation via nrf2 synthesis (mediated by B-adrenergic synthesis).

Where Serotonin depends only on tryptophan availability for activating its functions for Alleviating Oxidative Damage. Serotonin basically originated from tryptophan Tph1 (TGG), while Tph2 responsible for serotonin productive functions in brain (the binding of thymine T to GG which is so necessary to form proper serotonin. that it looks to me that Glucocorticoids (regulated by GPCRs) are the basis for regulating both B-arrestins but serotonin are fully connected to Trp availability for its synthesis that has the role of activating GTPase which is necessary for OPA1 repairs too and necessary for migrating serotonin to brain for activating Leu pentapeptides and Met pentapeptides in enkephalin brain tissue that it's cleared now that serotonin followed by melatonin has the role of activating Nrf2 (mediated by B-arrestins and B-adrenergic production) for adopting antioxidative stress and protecting brain functional activities and for repairing brain tissue upon activating both Ang2-AT2 and VEGF-A necessary for anti-inflammatory growth. So serotonin is having the role of activating both B adrenergic and Nrf2 (mediated by glucocorticoids and B-arrestins synthesis via NR4As pathway) for adopting antioxidative pathway and for activating both Ang2-AT2 and VEGF-A for running anti-inflammatory growth for protecting both of heart and brain functions . That it has been reported that: Nrf2 regulates NGF mRNA induction by carnosic acid in T98G glioblastoma cells and normal human astrocytes [51].

Where, NGF regulated by Ang2-AT2 and VEGF-A synthesis that as NGF activated as will reflect increasing in Ang2-AT2 and in VEGF-A synthesis [52]. And, Keap1 activates Nrf2 signaling protect myocardial cells from oxygen glucose deprivation/re-oxygenation-induced oxidative injury [53].

That the myocardial protection from oxygen glucose deprivation/re-oxygenation-induced oxidative injury runs by Nrf2 through activating Ang2-AT2 and VEGF-A for activating heme oxygenase and heme Biosynthesis through running anti-inflammatory growth, where NO and NO donors (NO mechanism) serve as a signaling molecule in the modulating tissue stress response and protect tissue from oxygen glucose deprivation.

Furthermore, Grape seed proanthocyanidin extract (GSPE) showed neuroprotective effects on the bladder of diabetic rats, as shown by the increased expression of nerve growth factor (NGF) and decreased expression of the precursor of nerve growth factor (proNGF) [54]. It's clear that Grape seed proanthocyanidin extract "GSPE" contains enough necessary amino acids as Glu, tryptophan, Thr, Ser which are having the roles of reactivating pyrimidine and purines kinases which are necessary for reactivating Estrogen productions from estradiol (from pro-inflammation and accumulated cholesterol) followed by activating glucocorticoid-beta and B-arrestins synthesis where GCs-beta begin to promote both mineralocorticoid and followed by B Adrenergic production which will activate Nrf2 synthesis for activating both Ang2-AT2 and VEGF-A synthesis which activate NGF with adoption to antioxidative functional activity with the concomitant adopting the elevation of downstream hemeoxygenase-1 (HO-1), where NO and NO donors (NO mechanism) serve as a signaling molecule in the modulating tissue stress response for protect from oxygen glucose deprivations and from its elevations too.

It has been reported that: compounds of triazine derivatives has the roles to increase nuclear level of stress sensing transcription factor, NF-E2 related factor 2, which contributes to redox homeostasis and cell survival following stress, and manage the modulation of oxidative stress-mediated disorders [55].

So triazine derivatives has a proper percentage of necessary amino acids including Glu and Leu that will activate Nrf2 synthesis and activate pyrimidine with purines kinases synthesis which can reactivate NR4As productive pathway. As Nrf2 are having the role of managing the modulation of oxidative stress-mediated disorders as Nrf2 are having the role of adopting the activation of Ang2-AT2 and VEGF-A synthesis for correcting the oxidative disorders throughout managing the anti-inflammatory growth and cells survival by VEGF-A productions functions.

The neuroprotection process which done by B-arrestins, and Nrf2 productive functions are mediated by specific stimulated processes for stimulating their basic protein kinases synthesis as pyrimidine and purines kinases synthesis for Paving the way for running OPA1 repairs and refunctioning the accumulated cholesterol, estradiol and pro-inflammatory molecules for reactivating estrogen synthesis which will promote GCs-beta synthesis and B-arrestins for running full anti-inflammatory growth and process for protecting cellular functional activity and adopt their functions. That triazine (may has enough necessary amino acids Glu, Ser, Pro tryptophan, … Specifically Glu which has the role of reactivating Leu which necessary for Nrf2 productive functions) has the role of reactivating OPA1 function for activating NR4As productive pathway for GCs-beta synthesis followed by Nrf2 synthesis for adopting heme oxygenase and adopt the both Ang2AT2 and VEGF-A production.

Triazine derivatives are having protective effect for neurons by modulating oxidative stress and Up-regulation of hemeoxygenase-1, glutamylcysteine synthetase glutathione peroxidase and nuclear factor-erythroid 2 p45-related factor 2 (Nrf2), while they inhibit NF-κB and decrease lipid peroxidation [56].

The activation of RXRα primary active pathway are the important basis for acting and Adopting inflammation for producing IL17 (and prevent the accumulated IL6) for Acyl-COA-beta productions which necessary for GCs-beta synthesis which regulate B-arrestins and Nrf2 production (mediated by B-Adrenergic synthesis) followed by gene expression (which done by activating anti-inflammatory growth via VEGF-A productions) that absolutely activate NRF2 followed by both Ang2-AT2 and VEGF-A productions (upon ACE stimulation) are effective for fast adopting myocardial constrictions and protections from K and Na binding toxicity, and adopt (GPCRs) Ang1-AT1 ratio through activating Ang2-AT2 synthesis. That NR4As pathway has the roles of recruiting active pathway for adopting Alpha oscillations dominant rhythm in both the resting and active (and in pathogenic cases) brain?

I would like to give a little clarification about the mechanism of the activities of brain waves that how are working and related to NR4As pathway function: 1st /the Delta Brainwaves is the stimulation to Cox2 and ATPase function during high stress for yielding energy that will produce high inflammatory molecules that will stimulate NR4As productive functions for acting on inflammation that will produce estradiol upon synthetase functions followed by synthase function for Acyl-COA-beta production that will activate Estrogen productions followed by inhibition in glucocorticoids-beta production that will including yielding high-energy which characterized Delta brain waves, then after that point B-arrestins will be produced (and mineralocorticoid necessary for protecting heart layers from K and Na binding toxicity). Where B-arrestins as a adopter protein will adopt Nrf2 synthesis with adopting oxidative high activities by antioxidative adopting function, at that point the alpha brainwave will begin followed by stimulating ACE functions for Ang2-AT2 productions which adopt heart constriction and functions followed by VEGF-A synthesis that will activate cellular growth through anti-inflammatory growth then the alpha waves will be at its optimum level. But theta Brainwaves almost near or after alpha brainwave. That are Near The Stage Of Vivid, Dreamlike Super Creativity, Insight, Intuition and Inspiration that depend on the type of amino acids that built B-arrestins and Nrf2 followed by Ang2-AT2 and VEGF-A that Leu Tyr Ser, Thr, Cys, methionine are so important for yielding theta brainwave.

The activation of orphan nuclear pathway by the availability of Glu, Leu, Pro and tryptophan amino acids will activate NR4As productive pathway that will improve firstly DCs Interleukin-2 (IL2 which act on inflammation which produced by effects of Cox2 and ATPase due to pathogenic stages or due to stress) for producing IL6 which upon synthase will improved for producing IL17 which are so necessary for glucocorticoids-bet a synthesis (note the IL6 which produced firstly by NR4As activations are ideal for activating bot GCs-gamma and IFN-gamma which will improved to GCs-beta and IFN-beta upon synthase functions) then followed by B-arrestins and by B Adrenergic synthesis (in availability of tryptophan) respectively, that B-arrestins will activate the re-expression to Nrf2 which activate the adoption of ACE functions for Ang2-AT2 and VEGF-A synthesis. I would like to note that may some can believe that NR4As can be a repressor for Nrf2 functions but NR4As is the basic regulator for GCs-beta and Nrf2 productions which activate angiotensin synthesis that when Ang2-AT2 formed will show decreasing to the function ratio of Nrf2 functions (that it functions is already done for reactivating angiotensin and VEGF-A synthesis for anti-inflammatory growth), and also when GCs-beta reactivated through feedback will reflect temporarily decreasing in Nrf2 functional ratio due to the reactivation of of S6K and reactivation of both pyrimidine synthesis and hydrophobic acids synthesis followed by estradiol and then estrogen synthesis which followed by B-arrestins synthesis and then will be followed by reactivation of Nrf2 upon cellular responses and upon high oxidative processes.

NR4As necessary for activating Nrf2 function which are strongly regulated by Leucine synthesis which regulated by Glutamine amino acids

Nrf2 are strongly depending on Leucine amino acid which are formed by glutamine function for modulating cellular functional activities, growth, and antioxidant signaling pathway upon immune response [57]. The Nrf2 has the function of activating growth through 1st: reactivating Glu synthesis which upon degradation activate pyrimidine and purines kinases synthesis followed by activating nuclear orphan pathway for GCs-beta synthesis which followed by Ang2-AT2 and VEGF-A synthesis for adopting anti-inflammatory growth, 2ndly Nrf2 has the role of activating directly the adopted angiotensin and VEGF-A synthesis necessary for running anti-inflammatory growth. Leu regulates protein synthesis and dégradation via activating mTOR signaling, while. Glutamine (Gln) synergistically promotes mTORC1 activation with Leu via glutaminolysis and Leu absorption via an antiporter. However, Gln has also been shown to inhibit mTORC1 activity [58].

Also, L-leucine increases GDH activity and stimulates glutamate synthesis from different nitrogen sources by regulating mTORC1 [59]. Previous study indicates that Gln and Glu synthesis are important for stabilizing leucine stability and functions that both glutamine and leucine can recover and stabiliz each other by translation process:

GAA – Gln <¬¬translations¬>
CTT Leu
GAG – Gln <¬¬trsnslat¬> CTC Leu .

Also, Glutamate formation via the leucine-to-glutamate pathway of rat pancreas [60]. So it's important for Leu to protect and Preserve its functional pathways through activating Gln and Glu synthesis and preserve their productive functional pathways. So as Leu are so important for Nrf2 functions as Glu are so essential for Nrf2 and SESN2 productive functional pathways, and consequently the Glu and Leu necessary for activating antioxidative functions and activating both Ang2-AT2 and VEGF-A productions followed by activating stem cells functions for protecting liver heart and brain functional activities.

That it has been reported that: Activation of Nrf2-Antioxidant Response Element Mediated Glutamate Cysteine Ligase Expression in Hepatoma Cell line by Homocysteine [61]. So both glutamate and Leu functions are connected to each other and both can be considered as so important for activating Nrf2 functions and activating antioxidative functions. Where, NRF2 strongly activates cystine uptake coupled with glutamate excretion and glutathione synthesis, which increases consumption of intracellular glutamate [62].

Note, the activation of Glu (GAG & GAA) synthesis by Leu is an important steps that are necessary for activating ATPase and GTPase functions (by purines in Glu) where GTPase protect and recover OPA1 repairs, and the using both purines GAG & GAA in activating Ang2-AT2 and VEGF-A synthesis for activating anti-inflammatory growth. And Nrf2 activation facilitates metabolic reprogramming and mitochondrial adaptation, and fine-tunes the innate immune response [63].

Means Nrf2 productive functions can reflect suppressing to IFN-gamma and reflect IFN-beta synthesis (upon synthase which act on Acyl-COA-gamma (which are basis for GCs-gamma and Interferons-gamma) for producing GCs-beta followed by B-arrestins synthesis for reproducing Nrf2. Nuclear related factor 2 (Nrf2) is a basic leucine zipper transcription factor that is activated in response to inflammation oxidative stress, and cellular responses for adopting oxidative functions and stress by increasing antioxidant transcription levels [64]. And the following study indicated that optimum isoleucine improved flesh quality, partly due to the activation of antioxidant defense through the Nrf2 signaling pathway [65].

So, inhibition in isoleucine will reflect Inhibition in antioxidative process by inhibition in Nrf2 roles as antioxidant. And, in older

adults, leucine supplementation may improve muscle protein synthesis in response to lower protein meals [66].

So how leucine supplementation may improve muscle protein synthesis in response to lower protein meals?? That Leu can reproduce Glu amino acids upon translation which will improve protein kinases synthesis and cellular processes. That, Immune cells largely depend on glutamine availability to survive, proliferate, and function, and ultimately defend our body against pathogens [67]. So the necessity of availability of glutamine in immune functions increased Leu synthesis and Nrf2 productive functions and consequently activate NR4As productive pathway.

Also leucine is necessary for Nrf2 for initiating immune functions mediated by Ang2-AT2 and VEGF-A synthesis for anti-inflammatory growth. That it has been reported that: Nrf2 production regulate and innate immunity [68]. Leucine can stimulate protein synthesis (through reactivating Glu synthesis which promote protein kinases and promote OPA1 repairs) in skeletal muscle, and increase in leucine-related mitochondrial biogenesis and oxidative .processes .and can Directed tumour metabolism to a less glycolytic phenotype [69].

I would like to clarify that the Leu is the main regulator for Nrf2 functional where Glu functions is the main regulator to both Leu and Nrf2 that the increasing in Glu function will reflect increasing in Leu and Nrf2 functions, where as mentioned above that Leucine can stimulate protein synthesis in skeletal muscle upon Glu synthesis by translation, where Glu has the role of activate pyrimidine and purines synthesis upon its degradations upon primary oxidative processes that will accelerate protein Biosynthesis regulated by Proline functions.

So, we can now concluded that deficiency in glutamine followed by Deficiency in Leu will be result in the deficiency in Nrf2 antioxidative function followed by Deficiency in NR4As productive functional pathway that can be the main reasons for pathogenic evolutions.

Synthase effect on IL2, on IL4 prevent the accumulation of the pro-structure of IgE) antigen-induced IgE production but not IgE2 [70]. And at the same time the Activation of the Nrf2/antioxidant response pathway increases IL-8 expression [71].

Inhibition in Glu reflect Inhibition in Leu and consequently inhibition in Nrf2 that will be result of accumulation in IL6 and decreasing in IL17 which important for GCs-beta productions, and will reflect decreasing in OPA1 repairs (which regulated by GTPase that can be activated by both Glu and Trp functions) that will be the result of increasing in Breast Carcinogenesis. That it has reported that Glucocorticoids Induce Breast Carcinogenesis through Nrf2 Inhibition [72].

Glutamines are necessary for Nrf2 and SESN2 protection for activating B-cells and brain functions

The decreasing in SESNs means decreasing in Nrf2 and basically in Leu and in necessary hydroponic acids that important for antioxidant functions where decreasing in hydrophobic amino acids can reflect decreasing in OPA1 function followed by decreasing in estrogen with accumulation in cholesterol (with accumulation in estradiol) that can reflect defects in fat metabolism.

Also deficiency or sever decreasing in Nrf2 and in SESN2 can can reflect decreasing in both Glu and Leu decreasing in Ang2-AT2 synthesis too. That, diabetes reflect decreasing in estrogen synthesis with accumulation in cholesterol and pro-inflammatory molecules due to inhibition in OPA1 function and decreasing in the necessity amino acids which necessary for activating OPA1 function and reproducing protein kinases which necessary for regulating cellular functions, so diabetes reflect reduction in Nrf2 function and in SESNs functions. That SESN1 decreased in the skeletal muscle and SESN3 decreased in the liver and adipose tissue in patients with high-fat diet and diabetics [73].

Also, Nrf2-ARE pathway regulates induction of Sestrin-2 expression [74]. And at the same time Sestrin 2 Protein Regulates Platelet-derived Growth Factor Receptor β (Pdgfrβ) Expression by Modulating Proteasomal and Nrf2 Transcription Factor Functions [75]. And Sestrin 1 (SESN1) considered as a tumor suppressor in lymphoma [76]. That as described previously the Nrf2 repressed tumor as a part from antioxidative functions as SESN2 will have the same functional processes for representing tumor content.

So, 1 SESNs considered as a tumor suppressor in lymphoma by activating Nrf2 production which can act as antioxidants and activate Ang2-AT2 with VEGF- A for anti-inflammatory growth. Also, both sesen2 and Nrf2 vmcsn activate glutamine synthesis which is necessary for protein kinases production and necessary for mitochondrial OPA1 repairs and necessary for Stemness of Bone Marrow Mesenchymal Stem Cells too.
Glutamine GAA – Glu <¬>CTT Leu
GAG – Glu <¬> CTC Leu ¬¬¬> activate Nrf2 and SESENs synthesis.

Glutamine is essential for leucine synthesis (upon translation, so consequently imp for Nrf2 and SESN2 productive functions) and for Mesenchymal Stem Cells and Bone Homeostasis. While, both Proline (CCA) and Thr (ACC) are so important for activating Trp TGG synthesis which are so important for activating serotonin synthesis.

It has been reported that: The Glutamine Is Essential for Stemness of Bone Marrow Mesenchymal Stem Cells and Bone Homeostasis [77]. And also, glutamine- prevents high oxidative processes through activating Leu synthesis and Nrf2 synthesis for adopting oxidative processes and prevent accumulation of oxygen products. Where, glutamine-derived glutathione prevents accumulation of reactive oxygen species and thereby safeguards cell viability [78]. So, now it is clear that inhibition in glutamine will positively lead to accumulation in pro-inflammatn (which produced by Cox2 functions)¬¬> Psoriatic arthritis(PsA), and then.

It's clear also to note that Psoriatic arthritis (PsA) associated with liver fibrosis because Glu is necessary for Leu synthesis and migration
Glu "GAG, GAA" ¬¬¬> Leu "CTC, CTT" (upon translations processes) where Leu is so necessary for SESEN 2 synthesis and functions, so reductions in Glu will reflect reduction in Leu which is necessary for live and brain functions. And also, the Glucocorticoid deficiency causes transcriptional and post-transcriptional reprogramming of glutamine metabolism.

The role of serotonin in promoting melatonin which activate NR4As pathway for activating GCs-beta which activate B-arrestins followed by badrenogic necessary for Nrf2 synthesis and Ang2-AT2 VEGF-A

Firstly: it is considered that atherosclerosis can be exacerbated by high unadopted oxidative stress, that the stimulation of high stress with reduction in serotonin or melatonin synthesis will cause or reflect reduction reductions in activating glucocorticoids synthesis

and reduction in NR4A pathway that will reflect decreasing in lipid metabolism and reductions in estrogen which necessary for glucocorticoids-beta synthesis that will be result of accumulation of cholesterol and pro-inflammation.

So serotonin (which regulated by Tph TGG synthesis and availability) and its dependent melatonin have their strong roles in modulating high stress, memories and brain functions through activating glucocorticoids synthesis via NR4As pathway for running full adopted anti-inflammatory growth and the antioxidative functions through B-adrenergic and Nrf2 synthesis which promoted by glucocorticoids-beta synthesis via NR4As pathway.

That the pathway for modulating high stress through serotonin synthesis which will activate melatonin which will activate glucocorticoid-beta synthesis via NR4As pathway

Trp Tryptophan (TGG)

ACC – Thr ¬¬activate¬>TGG Trp ¬¬¬activate ¬> serotonin ¬¬>activate melatonin ¬¬> activate NR4A2 pathway for activating glucocorticoid-beta synthesis ¬¬>activate B-arrestins activate B Adrenergic activate Nrf2 synthesis activate ACE for both Ang2-AT2 and VEGF-A synthesis for anti-inflammatory growth, for activating brain function, and for activating memories growth.

Also, Tph TGG has imp roles for activating serotonin synthesis and activating the GTPase synthesis Which necessary for mitochondrial OPA1 repairs and so are so essential for reactivating NR4As productive pathway (that setotin increased the expression of heme oxygenase via Activating melatonin which will activate glucocorticoid-beta that will stimulate Nrf2 synthesis via NR4As pathway), and both serotonin and melatonin are so important for modulating high stress and activating memories growth through activating glucocorticoid-beta synthesis via NR4As pathway that will be followed by activating anti-inflammatory growth mediated by both Ang2-AT2 and VEGF-A synthesis.

Basically serotonin originated by tryptophanTph1 which originate from blood from Thr phosphorylation mTOR pathway that Thr Deficiency will give decreasing in serotonin and decreasing in brain functions. The availability of Trp - TGG) are so necessary for serotonin synthesis where also the Thr phosphorylation in mTOR pathway are so necessary for Trp synthesis through translation process where

ACC – Thr ¬¬¬>TGG Trp

And Proline (CCA) also so important for activating Trp synthesis for serotonin synthesis. And pyrimidine and purines kinases synthesis are promoting Proline and Threonine followed by Trp synthesis which necessary for serotonin and melatonin synthesis:

ACC – Thr ¬¬¬>TGG Trp

And Proline ACC¬¬>TGG Trp

That serotonin has the role of activating melatonin synthesis which promote GTPase synthesis and directed for mitochondrial OPA1 repairs for activating orphan nuclear pathway and running lipolesis and increasing fatty acids productions. Also GTPase +thymine ¬>TGG that can reactivate Trp synthesis (through feedback) for reactivating melatonin synthesis and serotonin productive functions.

So previous note is the answer of how serotonin adpot increasing in oxidations through its functions as antioxidant, moreover serotonin can stimulate and activate S6K that activate ribosomes and chromosomes repair which activate both ATPase and GTPase. So I can conclude clearly that serotonin contribute in the antioxidative function through its roles in adopting mitochondrial OPA1 repairs and that can be considered which necessary for regulating orphan nuclear pathway for running NR4As productive pathway.

The N-acetyl serotonin (NAS) significantly increased expression of heme oxygenase-1, NAD(P)H quinine oxidoreductase-1 and glutamate-cysteine ligase catalytic subunit as well as nuclear translocation of NF-E2-related factor-2 [79].

Also, serotonin plays a crucial role in regulating hepatic function and response to injury (through activating orphan nuclear pathway which regulated by OPA1 function which regulated by melatonin that produce cGMP then GTPase which necessary for reactivating OPA1 membrane functions). Serotonin Act as a neurotransmitter and as a neuroendocrine hormone, it regulates Autonomic nervous system input to the liver, blood flow by activating Ang2-AT2 and VEGF-A 7 (mediated by GCs-beta, B-arrestins and Nrf2) within the normal and healthy liver and also regulates the proliferation and function [80].

Where, serotonin as an autocrine neurotransmitter in the pineal gland and suggests possible modulatory targets for melatonin secretion [81]. And the melatonin biosynthesis is done through the Serotonin (5-hydroxy-tryptamine) is converted to melatonin through the sequential action of two enzymes, serotonin N-acetyltransferase (arylalkylamine N-acetyltransferase, or AANAT) and hydroxyindole-Omethyltransferase [82].

That Melatonin (hormone of darkness) has generated a great deal of interest as a therapeutic modality for various diseases particularly sleep disorders [83]. That it has been proven that Melatonin regulates glucocorticoid receptor: an answer to its antiapoptotic action in thymus [84].

So, I concluded that tryptophan is the basic for serotonin synthesis which modulate melatonin synthesis the hormones of darkness that melatonin promote regulate glucocorticoids-beta synthesis so indicated that GCs-beta is activated and formed due to darkness (upon Tph availability for serotonin synthesis) and at darkness the GTPase will be activated for OPA1 repairs and will activate NR4As productive pathway which will include GCs-beta synthesis. Where inhibition in Tph will result of inhibition in melatonin (which produced by serotonin) can be the main reason of inhibition in lipogenesis and inhibition in glucocorticoids and in B-arrestins due to reductions in nuclear pathway synthesis that will included inhibition in GTPase production.

That, chronic melatonin administration improved HFD-induced dyslipidemia and hepatic lipid accumulation in Syrian hamsters with HFD-induced dyslipidemia, which might have occurred through inhibiting the lipogenesis pathway [85].

And, due to the activation of melatonin to nuclear orphan pathway and promoting glucocorticoids synthesis the Melatonin reduces intramuscular fat deposition by promoting lipolysis and increasing mitochondrial function [86].

Where, glucocorticoids promote and regulate lipolysis that prevent lipid accumulation [87]. So in breif melatonin which promoted by serotonin protect OPA1 repairs and functions through GTPase production and promote NR4As productive pathway for promoting GCs-beta synthesis that will be the result of preventing Lipids accumulation by increasing lipolysis, followed by B-arrestins synthesis, B Adrenergic, and Nrf2 productions.

So serotonin can support the function of antioxidants through promoting melatonin production which activate GCs-beta synthesis

via NR4As pathway followed by B-arrestins, B adrenalic, and Nrf2 productions where Nrf2 activate ACE for activating Ang2-AT2 and VEGF-A synthesis for activating anti-inflammatory growth. That inhibition in melatonin which necessary for regulating GCs-beta, B Adrenergic, and Nrf2 synthesis via NR4A2 pathway can be the main reason for the visual memory deficits that included decreasing in GTPase productive functions which produced mainly by S6K1 Tph, Glu and Leu functions.

Where melatonin synthesis (which activate NR4As pathway for activating GCs-beta, B-arrestins, and Nrf2) will activate the glutamylcysteine (GLUTANYL-TGT & GLUTANYL-TGC) for activating glucocorticoid-beta synthesis upon Beta synthase oxidative functions via NR4As productive pathway followed by Nrf2 production and mediated by B-arrestins productions. That it has been reported that: melatonin induces the expression of γ-glutamylcysteine synthetase (γ-GCS) the rate-limiting enzyme of glutathione (GSH) synthesis, in ECV304 human vascular endothelial cells [88].

The role of Nrf2 in activating liver and protect heart function regulated by GCs-beta synthesis via activating Akt/GSK3β/ Fyn kinase axis

The Akt/GSK3β/Fyn kinase axis is included the TAT and TAC Tyr kinases which are so necessary for building the promoters in neuronal active genes and subunits and are so important for activating orphan nuclear pathway which promote NR4As productive pathway. The Nuclear factor E2 related factor 2 (Nrf2) is a basic leucine zipper transcription factor that is activated in response to inflammation for running antioxidant functions oxidative that will improve inflammation molecules for producing Interleukin-6, and IL17 which activate GCs-beta productions which followed by Nrf2 production which activate ACE for activating both Ang2-AT2 and VEGF-A synthesis for adopting both liver regeneration and myocardial heart functions.

That it has been reported that: the activation of Nrf2 is a promising strategy for enhancing functional liver regeneration [89]. And, Nrf2 deficiency causes damage to hepatic cell (from oxidative processes) and reduced albumin productions throughout deficiency in GCs-beta followed by deficiency in B-arrestins and decreasing in running angiotensin productions.

Nrf2 and its signaling pathways has roles against oxidative stress to protect hepatic cell from oxidative damage during development of common chronic liver diseases [90]. And Nrf2 mediates the modulations of drug metabolism through the expression of GCs-beta followed by IFN-beta and signaling proteins to regulate anti-inflammatory growth and processes.

That the activated Nrf2 mediates induced expression of an array of enzymes and signaling proteins to regulate drug metabolism, antioxidant defense, and oxidant signaling [91].

Also, Nrf2 specifically regulates IL-22 response through the regulation of antioxidant response for activating Acyl-COA-beta and GCs-beta productions which protect and activate liver activities. That Nrf2 specifically regulates IL-22 response in vivo. And Nrf2 acts through the regulation of antioxidant response element (ARE) binding motifs in target genes to induce or repress transcription [92].

And so indicating that the antioxidant modulations by Nrf2 are having necessary functions for modulation the improving of pro-inflammatory molecules by, IL17, and IL22. Productions, and Nrf2 has the roles of improving pro-inflammatory molecules for estradiol synthesis followed by estrogen production which activate GCs-beta synthesis for modulating B-arrestins and B Adrenergic expression followed by recover Nrf2 functional stability and followed by angiotensin2 and VEGF-A Biosynthesis for anti-inflammatory growth, reprogramming and adopting microphages functions, and activating heme oxygenase.

The activation of Nrf2 signaling in the liver prevent hepatocyte necrosis through prevents the accumulation and amplification of Interleukins through promoting the, IL17, and IL22 productions which activate GCs-beta synthesis followed by B-arrestins and Nrf2 productions necessary for activating anti-inflammatory processes mediated by activating the running of angiotensin and VEGF-A synthesis. That cytoprotection of hepatocytes through Nrf2 signaling during inflammation prevents the amplification of inflammatory responses in the liver [93].

Also, the pyrimidine and purines kinases which produced by Glutamine degradations (by GTPase functions) are necessary for activating Nrf2 where cysteine synthase can increase the Nrf2 active pathway for protective modulation and so increasing anti-inflammatory growth and processes. That it has been reported that the cardioprotective effects of H(2)S are mediated in large part by a combination of antioxidant and antiapoptotic signaling [94]. That those combination of antioxidant and antiapoptotic signaling are the activations of NR4As productions followed by Nrf2 production and mediated by glucocorticoid-beta and B-arrestins synthesis and followed by activating Ang2-AT2 and VEGF-A synthesis for cardio-protections. The selenoproteins which are essential for thyroid hormone metabolism, are essential for maintaining oxidative homeostasis in erythrocytes and protecting against hemolytic anemia [95].

So as Trsp: Nrf2 double deficiency exacerbates anemia and increases intracellular hydrogen peroxide levels in erythroblasts as indicate the presence of cystathionine β-synthase can prevent the accumulation of H2O2 through H2S synthesis from selenoproteins which contains cysteine that increase Nrf2 functional pathways mediated by ROR beta synthesis which necessary for GCs-beta (where indicate that selenoproteins activate thyroid hormone metabolism mediated by Nrf2 activation). Also previous studies indicated that Cys and Leu reveal necessity for activating Nrf2 functional pathways.

And also, Fyn kinase enzymes which is member of the protein-tyrosine kinase and control cells growth are necessary for activating Nrf2 pathway via modulation of Akt/GSK3β/Fyn kinase axis, that Akt–Fyn kinase Regulate Nrf2 stability and the PHLPP2 controlled Nrf2 stability [96].

So, Gln, Cys, Leu, and Tyr kinases are necessary for activating Nrf2 via modulation of Akt/GSK3β/Fyn kinase axis for heart , liver protection and for running anti-inflammatory growth through activating glucocorticoid-beta and activating angiotensin synthesis followed by VEGF-A synthesis for running the adopted anti-inflammatory growth.

And also the glutamate-cysteine ligase, and glutathione peroxidase-2 were expressed only in Nrf2-enhanced mice, suggesting that Nrf2 activation prevents oxidative stress and acute liver injury through modulation of antioxidant defense-associated genes [97].

It's imp to note that estradiol and Estrogen production can reflect increasing in the antioxidant processes, that the estrogen synthesis from estradiol reveal the proper OPA1 functions and reveal the IL17 productions (from IL6 which produced by NR4As) that necessary for glucocorticoids synthesis and reveal the proper lipogenesis. That it has been reported that Estrogen-2 "E2" increased ARE activity >14-fold and enhanced the action of the Nrf2 activators, tertiary [98].

So, previous study indicated that the estrogen synthesis activate glucocorticoid-beta synthesis which enhance and regulate Nrf2 synthesis. Which will activate anti-inflammatory growth through activating ACE functions for Ang2-AT2 and VEGF-A productions. That it has been reported that Nrf2 Deficiency Upregulates Intrarenal Angiotensin-Converting Enzyme-2 and Angiotensin 1-7 Receptor Expression [99].

And, it has been reported that: Activation of Nuclear Factor-E2-Related Factor 2 (Nrf2) may be induced by cooperation of Nrf2 stabilization and leading to enhanced nuclear transport and stability of Nrf2 [100].

Note, L-Glutamate and Insulin Enhance Glycogen Synthesis (and vice versa), and, glutamine promotes muscle glycogen [101-102]. That glutamate enhance Leu synthesis and stability for stabilizing the Nrf2 functions, where Nrf2 is the important steps for activating The retinoic acid-related orphan receptors ROR-beta pathway which is the mediator steps for Nuclear hormone receptors synthesis followed by glucocorticoid-beta synthesis (which widely expressed in liver, thymus, brain, myocardial layer, and in skeletal tissue) which regulate immune functions by adopting anti-inflammatory growth, and also adopt or regulate the stress responses. And so the deficiency in Nrf2 will reflect deficiency in GCs synthesis that will lead to deficiency in immune survival which linked to the over expression of inflammatory cytokines.

Also, RORα is the step produced by Ang2-AT2 and VEGF-A production which mainly regulated by both B Adrenergic and Nrf2 functions and basically regulated by glucocorticoid-beta productions via NR4As pathway. That it has been reported that: RORα inhibits pathological cardiac hypertrophy [103]. And the activation of Nrf2 provides a novel mechanism to protect heart against pathological cardiac hypertrophy and heart failure via suppressing [104].

So ROR-alpha synthesis is activated by Nrf2 for anti-inflammatory growth which mediated and activated by Ang2-AT2 and VEGF-A productions (and basically controlled and regulated by glucocorticoid-beta synthesis via NR4As functional pathway). So Nrf2 regulated by NR4As productive pathway which activate first GCs-beta productions followed by B-arrestins synthesis (upon synthase function), where Nrf2 synthesis are a Suppressor to pathological cardiac hypertrophy Mediated by protecting heart from K and Na binding toxicity through mineralocorticoid synthesis (regulated by GCs-beta) and at the same time Nrf2 production activate ACE for the Ang2-AT2 production from the Ang1-AT1 which adopt heart constriction and functions followed by VEGF-A which important for anti-inflammatory growth. It's important to note that angiotensin II-induced cardiac hypertrophy just only in the case of Deficiency in some of hydrophobic amino acids as Leu, Tyr…and also can induce hypertrophy in the decreasing in both GCs-beta and B-arrestins synthesis with increasing in Ang1-AT1 percentages related to Ang2-AT2 productions.

The role of arachidonic acids in activating GCs-beta followed by modulating Nrf2 production

It is also looks that Arachidonic acid (AA) activate SESN2 functions mediated by Nrf2 synthesis too, that arachidonic acid is active biological tool that accelerate the GCs-beta synthesis upon activating OPA1 synthase functions. That it's so important to clarify the importance of arachidonic acids in activating Glucocorticoids-beta synthesis which has main roots in promoting and activating Nrf2 production which necessary for activating SESN2 synthesis which carry importance roles in protecting liver, brain and bones functions through protecting and increasing the anti-inflammatory processes and growth (mediated by GCs-beta functions and B-arrestins synthesis).

Where, The unsaturated fatty acids {arachidonic acid (AA)} are strong activator for accelerating GCs-beta followed by IFN-beta synthesis upon the OPA1 membrane functions that accelerate DCs functions for adopt the Interleukin-2 production (mediated by Leukotriene B4 production) which can be modified by synthase for activating GCs-beta followed by interferon-beta (IFN-beta) productions which accelerate anti-inflammatory processes and growth mediated by GCs-beta synthesis which accelerate both Ang2-AT2 and VEGF-A productions upon B-arrestins and ACE functions which adopt and filter glycoprotein and glycopeptides percentages for running angiotensin active pathway [105].

That as the Arachidonic Acid found as will stimulate first OPA1 synthase that will act on the pro-inflammatory molecules for activating estrogen folowed by GCs-beta productions which will activate the Nrf2 synthesis.

That, Arachidonic acid inhibits inflammatory responses through Binding to TLR4 co-receptor, myeloid differentiation factor 2 (MD2) and prevents saturated fatty acids synthesis [106]. So first steps for the function of AA activity is reducing the accumulation of pro-inflammatory molecules throughout estrogen and Acyl-COA-beta synthesis upon synthase function which directly followed by GCs-beta synthesis which promote both Nrf2 synthesis and IFN-beta synthesis in several pathways. That, Arachidonic Acid activate GCs-beta which activate Nrf2 synthesis (mediated by B-arrestins and G adrenergic synthesis) for activating heme oxygenase. That it has been reported Arachidonic Acid Induces ARE/Nrf2-Dependent Heme Oxygenase-1 Transcription [107].

And, 5-hydroxyeicosatetraenoic acid (5-HETE) and 5-hydroxyeicosapentaenoic acid (5-HEPE) are produced by 5-lipoxygenase (5-LOX) from arachidonic acid (AA) and eicosapentaenoic acid (EPA) that 5-HETE works as activator to Nrf2 productions [108]. So, Arachidonic Acid activate Glucocorticoids-beta for modulating Nrf2 production that activate its own adopted growth function through activating VEGF-A productions which necessary for activating anti-inflammatory growth. Where Arachidonic acid is strong activator for synthase function for producing Acyl-COA-beta from Pro-inflammatory molecules (which produced upon Cox2 functions) that AA activate 5-Lipoxygenase which produce 5-HETE that considered as works as activator to Nrf2 productions and consequently to SESN2 synthesis for modulating hypoxia and reducing or modulating the oxidative processes produced by Cox2 and ATPase whatever during infection or due to high stress.

Nrf2 is necessary for Adopting anti-inflammatory growth and cardiac Functions and protection

Nrf2 synthesis has basic roles in cardiac protection and function too. That it has been reported that, Patients with insufficient Nrf2

levels in their cardiovascular system are more vulnerable to heart failure "HF" development [109].

And, it has reported that Ang II-induced cardiac remodeling and HF rat model, allicin treatment could prevent the development of cardiac remodeling and the progression of cardiac hypertrophy to cardiac dysfunction, by enhancing the Nrf2 pathway [110]. And, Nrf2 are indicated in playing a role in different aspects of cardiovascular disease [111].

And, Nrf2 is crucial for cardiac adaptation [112]. So Nrf2 regulated firstly by GCs and B-arrestins and B Adrenergic synthesis then regulate the Ang2-AT2 productions upon ACE activation for increasing and adopting cardiac functions and preventing the accumulation of Proinflammatory cytokines (upon Cox2 and ATPase oxidations) and protect heart and muscles from toxicity through mineralocorticoid productions.

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Also, it has been reported that: nhibition of NRF2 could be an important by viral tactic to ensure efficient propagation [113]. Its clear that NRF2 generally has cyto-protective functions (but in the availability of glutamine and Leu amino acids) that can protect against virus-induced cell death and subsequent inflammation-induced immunopathology mediated by GCs-beta synthesis.

The Stimulation of immune cells with Toll-like receptor (TLR) ligands such as lipopolysaccharide (LPS) results in NRF2 activation which reduce pro-inflammatory cytokines [114].

Also the effect of Nrf2 on macrophage metabolism reveal how Osteoarthritis OA can be treated through reprogramming macrophage functions [115]. The effect of Nrf2 on macrophage functions reveal OA can be treated through activating NR4As productive pathway for activating GCs-beta which is so important for activating both Nrf2 and angiotensin Biosynthesis which are so important for anti-inflammatory growth and can modulate Reprogramming macrophages synthesis and functions. And there is an inverse relationship between the ratio of Nrf2 expression and the viral entry/replication, that supplementation with Nrf2-activating antioxidants inhibits viral replication in human NEC [116].

And, Nrf2 regulatory pathways represent novel therapeutic targets for cardiac protection [117]. So, Nrf2 has basic roles for cardiac protection through activating by GCs-beta synthesis which promote mineralocorticoid synthesis for protecting hart layers from K and Na binding toxicity. And, NRF2 drives the cell cycle entry and differentiation, that appears to be beneficial for recovery from blood loss (through activating both Ang2-AT2 and VEGF-A synthesis) [118].

The role of S6K in cells growth and in Nrf2 synthesis

P70S6K plays a critical role in the signaling pathways by which AII induces hypertrophy of vascular smooth muscle cells [119]. V-ATPase activity is required for the S6K activation (where S6K required for ribosomes repairs) [120]. And, β-Adrenergic agonists regulate Na-K-ATPase via p70S6k [121]. So S6K synthesis promote ribosomes repairs that activate ATPase which govern the pro-inflammatory synthesis which stimulate DCs for IL2 production and stimulate NR4As pathway for IL6 production which upon synthase wil activate IL17 which necessary for GCs which synthesis and Nrf2 which adopt Ang2-AT2 and VEGF-A synthesis for anti-inflammatory growth. Where also S6K activate GPCRs synthesis which necessary for activating GCs-beta synthesis.

It's Impor'ant to note that S6K is not suppressor to cells proliferation except contain mutation (due to decreasing in Gln, Leu, Tyr, Ser), that can reduce OPA1 synthase function and phospholipase. That specific mutation in S6K can cause mutations in IL2 that can be improved to produce IL30 and IL40 in other factors, but normal S6K with proper pyrimidine kinases are essential for activating estrogen synthesis (through activating OPA1 synthase) and for activating IL6 ¬¬>IL17 productions which essential for GCs-beta followed by IFN-beta and Nrf2 synthesis that can activate B-cells functions and self-renewal stem cells "STC "followed by anti-inflammatory growth. That, the S6k gene production regulates and govern cells size (due to enhancing GPCRs synthesis followed by enhance the NR4As productive pathway) [122].

S6K Is necessary for activating ATPase and GTPase which necessary for OPA1 repairs where that repair function necessary for repairing OPA1 enzymes includes synthase enzymes which necessary for producing Acyl-COA-beta which activate GCs-beta that consequently activate IFN-beta and anti-inflammatory processes.

That , Ras/Erk Signaling (which activated by S6K function) are Essential for Activating Protein Synthesis by Gq Protein-Coupled Receptor [123].

Where GPCRs are essential for GCs-beta productions and consequently for Nrf2 synthesis. And In fact, increased growth of hormone-stimulated maize axes was positively correlated with an enhanced rpS6 phosphorylation [124]. So, in bref thé synthesis of S6K are necessary for modulating ATPase and GTPase production which necessary for OPA1 repairs followed by modulating GPCRs production which necessary for GCs-beta synthesis (upon synthase function) that GCs-beta are the basis for modulating Nrf2 synthesis and functions followed by SESN2 synthesis.

The roles of Leu in modulating Nrf2

Nrf2 belongs to CNC ("cap 'n' collar") subfamily of the basic region-leucine zipper transcription factors family. That he locus control region of the beta-globin gene is composed of four erythroid-specific hypersensitive SITES (HS-2) , that the HS-2 has a powerful enhancer and contains a tandem repeat sequence for the transcription factors AP1 and NFE2 (activating protein 1 and nuclear factor erythroid 2, respectively) [125].

Within Nrf2 are 605 amino acids act as seven highly conserved functional NRF2-ECH homology. The Leu synthesis with other necessary hydrophobic acids through Proline functions and mediated by synthetase functions for pyrimidine synthesis are so important for cells proper metabolism and for anti-inflammatory growth. That leucine polymer loaded DOX (Leu-DOX) induced much less autophagy (in myeloid leukemia which contains mutation in their content) but more robust apoptosis in AML cells [126]. And, leucine has been found to promote protein synthesis and decrease protein degradation via activating mTORC1 biosynthesis [127].

That has been reported that: the presence of isoleucine seems to affect majorly Tregs, rather than conventional T cells [128]. That isoleucine by itself will not activate Treg functions but the mechanism of activating Treg and neuronal function will done by activating Nrf2 where its function dependent on Leu followed by the function of Nrf2 on adopting antioxidant functions followed by directly activating Ang2-AT2 and VEGF-A productions - via Activating ACE functions) that will activate anti-inflammatory growth includes B-cells and T-cells functional activities and immune survival.

Also Leu will Activate glutamine synthesis which activate protein kinases synthesis through activating S6K and mTORC1 productions, where pyrimidine kinases and S6K promote GCs-beta functions which promote B-arrestins which activate the ACE for adopting angiotensin for VEGF-A productions which necessary for running the adopted anti-inflammatory growth and prevent anemia.

That it has been reported that L-leucine improves the anemia via activating the mTOR pathway [129]. Also, dietary restriction of leucine caused a significant decrease in the lysis of tumor cells by lymphocytes. Likewise, decreased concentrations of BCAAs, commonly seen in patients with advanced liver cirrhosis, were associated with impairment of the function and maturation of dendritic cells [130].

The Ser phosphorylation and leucine are so important for pyrimidine kinases which important for Nrf2 synthesis which regulate sesen2 synthesis. That it has been reported that The Phosphorylation of Nrf2 at Ser-40 by protein kinase C (which promoted and activated by leucine) regulates antioxidant response [131]. Where Sestrin2 Is a leucine sensor promoted by mTORC1 pathway [132].

Conclusion

The activation and increasing in Estrogen-2 expression will activate glucocorticoid-beta synthesis followed by increasing in the ARE activity "more than 14-fold" for activating Ang2-AT2 and VEGF-A synthesis that enhanced and mediated by the expression of Nrf2 via NR4As pathway. The Serotonin has necessary role for supporting the function of antioxidants through promoting the melatonin production which has the role of activating GCs-beta synthesis via NR4As pathway followed by B-arrestins, B adrenalic, and Nrf2 productions where Nrf2 activate ACE for activating Ang2-AT2 and VEGF-A synthesis for activating anti-inflammatory growth and heme oxygenase. That inhibition in melatonin which necessary for regulating GCs-beta, B Adrenergic, and Nrf2 synthesis (during modulations of antioxidative stress via NR4A2 pathway) can be the main reason for the visual and memory deficits that included decreasing in GTPase productive functions which produced mainly by S6K1, Tph, Glu, and Leu functions.

The serotonin plays a crucial role in regulating hepatic function and response to injury (through activating orphan nuclear pathway that activate cGMP then GTPase which necessary for reactivating OPA1 membrane functions) through activating melatonin followed by GCs-beta synthesis and Nrf2 productions via NR4As pathway then followed by activating Ang2-AT2 and VEGF-A synthesis for anti-inflammatory growth. Serotonin Act as a neurotransmitter and as a neuroendocrine hormone, is regulating Autonomic nervous system input to the liver, blood flow by activating Ang2-AT2 and VEGF-A (mediated by melatonin synthesis which activate GCs-beta, B-arrestins and Nrf2 productions via NR4As pathway) for regulating anti-inflammatory growth. Melatonin plays a critical role in the pathophysiological process including circadian rhythm, apoptosis, and oxidative stress. It can be synthesized in ocular tissues, and its receptors are also found in the eye that has effective roles in adopting and improving vision, that inhibition in melatonin synthesis (regulated by Tph TGG) will be result of inhibition in modulating antioxidative stress that can be the result of glioblastoma multiform located in posterior corpus callosum.

The activation of melatonin synthesis (which activate NR4As pathway for activating GCs-beta, B-arrestins, and Nrf2) will associated by the glutamylcysteine (GLUTANYL-TGT & GLUTANYL-TGC) for activating glucocorticoid-beta synthesis upon Beta synthase oxidative functions via NR4As productive pathway followed by Nrf2 production and mediated by B-arrestins and B-Adrenergic productions. And, it's clear that Recirculating B cells (and modulating high stress and activating memories will be done by activating melatonin synthesis "which regulated by serotonin synthesis" for activating glucocorticoids synthesis via NR4As pathway) will be done through activating NR4As productive pathway for activating glucocorticoid-beta For activating anti-inflammatory processes mediated by B-arristin synthesis which activate Beta(2)-adrenergic production for activating Nrf2 production for activating "respectively" Ang2-AT2 and VEGF-A synthesis for running anti-inflammatory growth includes bone growth.

The Nuclear factor E2 related factor 2 (Nrf2) functions depend on leucine (and Leu functions are depending on activating glutamine synthesis and functions for stabilizing Leu and Nrf2 functions) and activated in response to inflammation for running antioxidant functions oxidative that Nrf2 produced upon B-arrestins regulation and GCs-beta regulations via NR4As pathway, that Nrf2 will improve inflammation molecules for producing Interleukin-6, and IL17 which activate GCs-beta productions which followed by Nrf2 production which activate ACE for activating both Ang2-AT2 and VEGF-A synthesis for adopting both liver regeneration and myocardial heart functions.

Nrf2 is crucial for cardiac adaptation through its antioxidative function and it's activate to ACE for adopting Ang2-AT2 and VEGF-A synthesis which adopt myocardial constriction and adjust the Ang1-AT1 ratio. And also B-arrestins regulate B-adrenergic which regulate and adopt Nrf2 expressions, that Nrf2 has a critical roles in treating inflammatory disease and Osteoarthritis "OA" through its important roles in reprogramming macrophage functions. Also, the Psoriatic arthritis (PsA) associated with liver fibrosis because Glu is necessary for Leu synthesis and migration.

Glu "GAG, GAA" ¬¬¬> Leu "CTC, CTT" (upon translations processes) where Leu is so necessary for SESEN 2 synthesis and functions, so reductions in Glutamine will reflect reduction in Leu and reduction in Nrf2 which is necessary for liver, for heart function and for brain functions, notice that: glucocorticoids synthesis via NR4As pathway has the role of reactivating glutamine functional processes for reactivating and re-stabilizing the Nrf2 functions. And in conclusions the Nrf2 regulated by NR4As productive pathway which activate first GCs-beta productions followed by B-arrestins synthesis (upon synthase function), and B Adrenergic synthesis which promote Nrf2 production "respectivily", where Nrf2 synthesis are a Suppressor to pathological cardiac hypertrophy Mediated by protecting heart from K and Na binding toxicity through mineralocorticoid synthesis (regulated by GCs-beta) and at the same time Nrf2 production activate ACE for the Ang2-AT2 production from the Ang1-AT1 which adopt heart constriction and functions followed by VEGF-A which important for anti-inflammatory growth.

The neuroprotection process are done by B-arrestins, and Nrf2 productive functions which are associated by specific stimulated processes for stimulating their basic protein kinases synthesis as pyrimidine and purines kinases synthesis which activated by Glutamine and leucine synthesis which activate Nrf2 functions, that glutamine synthesis are associated with activating GTPase productions which activated by tryptophan (during activating both serotinin and melatonin for modulating antioxidative stress) where previous process will be included preventing the accumulated

cholesterol, estradiol through reactivating estrogen synthesis which will promote GCs-beta synthesis and B-arrestins for running full anti-inflammatory growth and process for protecting cellular functional activity and adopt their functions.

Leucine has the role of to promoting protein synthesis, and isoleucine affect by reactivating the majorly of Tregs ,that isoleucine by itself will not activate Treg functions but the mechanism of activating Treg and neuronal function will done by activating Nrf2 where its function dependent on Leu followed by the function of Nrf2 on adopting antioxidant functions followed by directly activating Ang2-AT2 and VEGF-A productions – via Activating ACE functions) that will activate anti-inflammatory growth includes B-cells and T-cells functional activities and immune survival.

Also Leu will Activate glutamine synthesis which activate protein kinases synthesis through activating S6K and mTORC1 productions , where pyrimidine kinases and S6K promote GCs-beta functions which promote B-arrestins which activate the ACE for adopting angiotensin for VEGF-A productions which necessary for running the adopted anti-inflammatory growth, heme oxygenase and prevent anemia. That L-leucine via Activating Nrf2 functions prevent the anemia via activating S6K and mTORC1 production for protein kinases production followed by estrogen synthesis for reactivating glucocorticoids synthesis via NR4As pathway.

Conflict of interest

The Author declare that this 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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