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Lysine and Tryptophan have the Protection Basis against Lysosomal Dysfunction and both PKU and CVD including Mitochondrial Disorder Mediated by Activating Lysosomes and OPA1

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ABSTRACT

The phenylketonuria "PKU" due to sever decreasing in lysine "AAG" and in Lys/ phosphorylation (which necessary for lysosomal digestive function), and associated with sever decreasing in Trp "TGG", followed by mitochondrial dysfunction and lysosomal dysfunction, that followed by sever decreasing in phe /hydroxylase and in Tyr/ hydroxylase, and followed by decreasing in lysine acylation and in SFACs productiin which followed by decreasing in RA productive pathway and associated with increasing in both of TNFa and cholesterol accumulation which activate increasing in in both of TNFa and NLRP3 pathogenic pathway which reflect decreasing in estrogen synthesis and in dopamine production, that followed by increasing in the risk of ischemic damage pulmonary disease and diabetes.

And we can conclude that both of Lys "AAG" and Trp "TGG" are so necessary for activating mitochondrial oxidative functions and necessary for promoting transport system where Mitochondria is so necessary to activate antioxidant function and promoting all of Phe hydroxylase, Tyr hydroxylase, and Lys acylation production which necessary for dopamine and RA synthesis respectively, where the PKU characterized by sever decreasing in antioxidant function, and sever decreasing in both Phe/ hydroxylase & Trp/ hydroxylase production, followed by decreasing in dopamine production and decreasing in retinoic acid production (which due to the reduction in SFACs synthesis).

And I concluded that PKU characterized by sever decreasing in Phe /hydroxylase and Tyr /hydroxylase, followed by reduction in dopamine production, and reduction in alpha amylase, that associated with increasing in TNFa and in NLRP3 pathogenic pathway, and associated with increasing in the pulmonary disease and CVD risk.

Retionic acid "RA" is regulated by lysine acylation and is regulated by lysine acylation mediated by short fatty acid synthesis, which regulate aminoacyl-tRNAs production regulated by mitochondrial enzymes and regulate mRNA production by E coli (regulated by phenylalanine) that necessary to run antioxidant functions and cellular biosynthesis.

The antihypertensive pathway mechanism is: the Lysine →activate ATPase and both lysosomes and Mitochondrial oxidative functions which activate lysine acylation →activate short fatty acid synthesis →stimulate retinoic acid "RA" synthesis - →where both Lys and Trp activate GTPase which promote mitochondria repair and oxidative functions, which activate, Phe/ hydroxylase, and activate Tyr/ hydroxylase which activate dopamine, followed by activating NR4As pathway which responsible for activating GC-beta and both of Oxytocin and Nrf2, followed by Ang2-AT2 and VEGF-A productive functions and heme oxygenase production (notice dopamine regulate heme oxygenase mediated by dopamine beta-hydroxylase which regulated by Mitochondrial oxidative functions) followed by activating anti-inflammatory growth and processes.

Lysine Methylation has important role to enhance and adopt hypertension through activating RA and pervious Antihypertensive pathway mediated by Phe/hydroxylase synthesis and Tyr /hydroxylase production followed by activating both of dopamine and NR4As pathway.

Where dopamine synthesischaracterized by activating Antioxidant functions that prevent cholesterol accumulation, and in turn increase the estrogen production (which it's synthesis reflect potential protection from pulmonary disease), and activate the NR4As pathway which regulate all of Oxytocin, Nrf2 production, followed by Ang2-AT2 and VEGF-A production, which followed by activating heme oxygenase and anti-inflammatory growth and processes that prevent LV-hypertrophy, and prevent coronary calcification.

Also, the increasing in Lys AAA with decreasing in both of Lys AAG and decreasing Trp TGG will cause decreasing in lysosome proper function, and Pero cause Decreasing in GTPase and decreasing in the Mitochondrial oxidative functions, that will cause decreasing in Phe hydroxylase and in Tyr hydroxylase followed by decreasing in lysine acylation, and associated with increasing in cholesterol accumulation, and also associated with decreasing in both of IL17 production and estrogen functional pathway, that will increase the risk of T2D, pulmonary disease, and increase the risk of PKU and CVD.

Both Lys and Trp are necessary to activate transport across cells membranes, that activate antibacterial function and anti-atherosclerosis, mediated by activating lysosomes and OPA1 oxidative functions, where OPA1 functions activated by GTPase productive functions which play important role in activating transport system pathways within and between cells.

Lysine acylation is playing important role in activating SFACs production and RA synthesis which protect from pulmonary disease and from ischemic damage.

Both Lys and Trp are having the Potency to activate lysosomes and Mitochondrial oxidative functions which activate lipid and protein digestion and enhance Phe /hydroxylase and Tyr / hydroxylase, followed by activating lysine acylation which activate SFACs production and promote the RA synthesis and enhance antioxidant functions and anticoagulant functions, followed by dopamine synthesis and protection against ischemic damage and against both of diabetes, pulmonary disease, CVD and PKU.

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Methods and Results

The Lysosomal dysfunction is associated with increasing in undigested polymers, and decreasing in both E coli and in aminoacyl tRNAs (which regulated by lysine acetylation) productive functions, followed by decreasing in mRNAs (production by E coli) which followed by decreasing in both anti-inflammatory processes and decreasing in heart functions, and followed by increasing in TNFa which activate the increasing in NLRP3 inflammasome pathogenic functions.

Lysine "AAA, AAG" is necessary amino acids for activating lysosomes digestive functions, and necessary to promote both of ATPase and GTPase productive functions, that GTPase necessary to promote mitochondrial oxidative functions, while mitochondria are so necessary for activating Phe /hydroxylase and Tyr /hydroxylase (where Tyr hydroxylase activate dopamine production), that prevent the cholesterol accumulation and prevent the increasing in TNFa, followed by enhancing the activation of antioxidant function which mediated by activating Phe/ hydroxylase and Tyr/ hydroxylase which regulate dopamine production, then followed by activating NR4As productive pathway which regulate all of GC-beta, B-adrenergic, oxytocin and Nrf2 production.

Decreasing in both of lysine, and Trp, cause mitochondrial dysfunction, and Lysosomal dysfunction followed by increasing in TNFa and appearance of incurable medical cases:

Lysosomal dysfunction associated with deficiency in Lysine phosphorylation, followed by decreasing in mitochondrial functions and decreasing in both of Phe/hydroxylase and Tyr/ hydroxylase which followed by decreasing in E coli functions and decreasing in aminoacyl-tRNAs production, then followed by decreasing in protein biosynthesis mediated by decreasing in mRNAs efficiency (which produced by E coli), and increasing in both of cholesterol precipitation, and undigested polymers precipitation in blood vessels, then their level in plasma will be elevated, that will cause PKU, diabetes, pulmonary disease and cardiovascular disease.

The lysosomes dysfunction is due to lysine dysfunction which associated with decreasing in Phe/hydroxylase productive functions which reflect decreasing in mitochondrial oxidative function and in Tyr/ hydroxylase, followed by decreasing in aminoacyl tRNAs production and decreasing in dopamine biosynthesis, that will lead to abnormal autophagy production and reduction in NR4A pathway that followed by reduction in the antioxidant functions. That, some studies reported: Defective lysosomes lead to abnormal autophagy, activation of inflammation, and reduction in the infection control [1].

The Lysosomal damage reflect increasing in the undigested polymers and reflect decreasing in GTPase and Mitochondrial dysfunction, that both of cholesterol and undigested polymers will be responsible for activating TNFa production which will activate the NLRP3 inflammasome.

That it has been approved that: the Lysosomal damage has been implicated in activating NLRP3 inflammasome in response to crystals or particulates [2].

So not only lysosomal dysfunction implicated in activating NLRP3 pathogenic pathway but also reduction in Lys AAG and Trp TGG are implicated in activating pathogenic NLRP3 pathway. Also, other studies approved that the Lysosomal dysfunction is associated with activating the NLRP3 inflammasome in chronic unpredictable mild stress-induced depressive mice [3].

So Lysosomal damage reflect increasing in undigested polymers and in cholesterol followed by increasing in TNFa which promote the NLRP3 inflammasomes activities, which will increase the risk of CVD.

The Increasing in NLRP3 reflect increasing in TNFa, and reflect severe reduction in both of lysosomal digestive functions and in mitochondrial oxidative function which cause decreasing in both of Phe /hydroxylase and in Tyr /hydroxylase that cause serious Pathogenic cases eg: diabetes, phenylketonuria, and CVD. That some studies reported that: Activation of Inflammation in Patients with Cardiovascular Disease Are Associated with Higher Phenylalanine to Tyrosine Ratios [4]. So patients with CVD in previous study indicated sever decreasing in Lys and in Trp followed by reduction in lysosomal function and reduction in mitochondrial oxidative functions which cause reduction in Phe hydroxylase and in Tyr hydroxylase (that cause accumulation to Phe and Tyr) increasing in NLRP3 pathogenic pathway.

Also, the lysine residues in cathepsin D were so important for phosphorylation as those in procathepsin L [5]. While, Lysine fatty acylation promotes lysosomal targeting of TNF-α [6]. So, we can conclude that as lysine fatty acylation biosynthesis activated, as TNFa will be decreased or will be inhibited, that mediated by proper activation to lysosomes and mitochondrial functions.

So, lysine is the major amino acid in cathepsin D that is so important for phosphorylation through activating both ATPase and GTPase which necessary for activating mitochondrial repairs and it's oxydative functions, and activate lysosome digestive functions, therefore prevent the accumulated cholesterol and then prevent the increasing in cholesterol and in both of TNFa and NLRP3, and prevent the aorta and B. vessels calcification.

Where, studies reported that: Lysine functions Prevents Arterial Calcification [7]. And, the altered CNS excitability due to decreasing in lysine which followed by lysosomal dysfunction and Mitochondrial dysfunction, which followed by increasing in cholesterol and in the undigested polymers which promote the increasing in TNFa production. That studies reported that: the Microglial activation and TNFα production mediate altered CNS excitability following peripheral inflammation [8].

And so, the lysosomal dysfunction (due to decreasing in lysine phosphorylation) is associated with decreasing in Lys acetylation and decreasing in Phe/hydroxylase (which due to decreasing in mitochondria oxidative functions), and then associated with increasing in TNFa, and followed by increasing in the risk of calcification, cardiovascular disease, and pulmonary diseases.

That, Also studies reported that: Lysine suppresses myofibrillar protein degradation by regulating the autophagic-lysosomal system through phosphorylation of Akt in C2C12 cells [9]. note that phosphorylation of Akt is the main for activating lysine Phosphorylation in lysosome that prevent or suppress myofibrillar protein degradation by regulating the lysosomal digestive functions.

Also, lysosome not only is a place for cargo degradation but also plays crucial roles in regulating macrophage polarization [10]. that macrophage polarization mainly regulated by both E coli and mitochondrial functions where their functions mainly controlled by lysosomal function which regulated by the Lys functional activities.

The lysine phosphorylation which activate Phe /hydroxylase and E coli functions is mediated by activating mitochondrial repairs and functions which mainly controlled by GTPase production (that Lys & Trp are having imporoles in activating GTPase production), where mitochondrial function necessary to activate IL17 production followed by glucocorticoid beta and β-arrestin production and followed by activating both of oxitocin and Nrf2 production (in availability of Leu, Cys, Tyr) to improve myocardial function through adopting glycemic optimal percentages, adopt protein glycation, and form own related macrophages productive functions which adopt anti-inflammatory growth and processes.

Where, studies reported that, L-Lysine is so important to Prevents Arterial Calcification (through activating lysosomal function and activating GTPase which promote mitochondria to prevent cholesterol and undigested polymers accumulation) [11].

Also, it has been approved that, Nrf2-mediated anti-inflammatory polarization of macrophages [12]. Now I would also like to clarify an important fact that: not only lysine important for activating the lysosome and mitochondria, but also the tryptophan is very important activator for lysosomal function and for mitochondrial oxidative functions through its important to activate the GTPase production that reactivate the mitochondrial repairs and function.

That it has been approved that: TRP channel 3 (TRPML3), a transient receptor potential cation channel localized to lysosomes. TRPML3 activation initiates lysosome exocytosis, resulting in expulsion of exosome-encased bacteria [13]. Trp has important role to activate lysosome phosphorylation by activating GTPase production which also has important role in activating mitochondrial repairs and functions, that TRP Channel has important role to Trigger Pathogens Expulsion by activating GTPase production which has the function to activate both lysosome and mitochondria. Also, that previous role of Trp to activate GTPase production can explain its role along the kynurenine (Kyn) pathway to prevents hyperinflammation and induces long-term immune tolerance [14].

So it's clear that both of lysine "AAG" and Tryptophan "TGG " amino acids are having so important roles to activate both of lysosomes digestive functions and mitochondrial repairs and functions, that both are responsible for preventing the accumulation of undigested and undigested polymers, then both of Lys and Trp responsible to activate mitochondria which responsible to activate both of IL17 and estrogen, and then are responsible for activating Phe hydroxylase and Tyr hydroxylase production (regulated by mitochondrial oxidative functions) that are protecting against PKU, pulmonary disease, diabetes, and CVD.

And, decreasing in both lysine and Tryptophan are connected to lysosomal damage that cause decreasing in mitochondrial oxidative function lead to decreasing in both of Phe /hydroxylase and Tyr/ hydroxylase production, that will cause decreasing in dopamine production and increases in the inflammation that will cause phenylketonuria and sever decreasing in antioxidant functions that cause pulmonary disease, ischemic damage and CVD.

Also, the activation of IL17 is by mitochondrial function will activate GC-beta production and then will activate both of Oxytocin and Nrf2, where Oxytocin alleviates liver fibrosis via hepatic macrophages [15]. Where, oxytocin stimulates the AMP-activated protein kinase pathway (AMPK) involve the autophagic processes, and may support the renewal of mitochondria [16].

So treatment by Lys AAG and Trp TGG will activate the mitochondrial oxidative functions which will activate the il17 which by itself will activate glucocorticoid-beta production via activating NR4As pathway which will activate oxytocin production, where, oxytocin synthesis can reduces the accumulation of proinflammatory cytokines and reduces immune cell infiltration. That Oxytocin stimulates differentiation stem cells to cardiomyocyte lineages as well as generation of endothelial and smooth muscle cells, promoting angiogenesis [17].

Also, as Trp is important for activating transport system through activating GTPase production which necessary for activating mitochondrial oxidative functions which activate Phe hydroxylase and Tyr hydroxylase and estrogen production that protect against pulmonary disease PKU and CVD) , as Trp is qualified treat CVD, pulmonary disease and PKU (where Trp activate Phe hydroxylase and Tyr hydroxylase that prevent their accumulation), where it has been approved that: Tryptophan metabolism important for treatment patients suffering from CVD [18]. So, CVD is due to sever decreasing in lysosomal functions that can be treated by tryptophan and by lysine "AAG" to which can activate both previous intracellular systems through activating lysosomes and OPA1 oxidative functions and activate transport system that will activate the proper recovery against CVD.

Notice that High tryptophan diet reduces extracellular dopamine, and can affect the dopamine levels and functions which will be discussed later. Where the reduction in both of Lys and Trp can cause Lysosomal dysfunction which is associated with increasing in TNFa and decreasing in VEGF-A.

The Lysosomal dysfunction induce apoptosis in chondrocytes through BAX-mediated mitochondrial damage [19]. So absence of Lys and Trp cause lysosomal dysfunction and Mitochondrial dysfunctions which cause apoptosis in chondrocytes.

And the mitochondrial dysfunction promises the increasing and accumulation in cholesterol and pro-inflammation that cause increasing in NLRP3 pathogenic pathway , that it has been approved that Chronic inflammation during IBD may be mediated by NLRP3 inflammasome activation [20]. So sever decreasing in lysine and Trp cause apoptosis in chondrocytes followed by increasing in the

cholesterol and in both inflammation which promote the activating TNFa which promote increasing in the pathogenic NLRP3 pathway.

And so in case of lysosomal dysfunction and Mitochondrial dysfunctions , the free Cholesterol-loaded Macrophages Are an Abundant Source of Tumor Necrosis Factor-α and Interleukin-6 [21]. And now, the Increasing in TNFa is related to increasing in cholesterol and related to the decreasing in both of mitochondria and to the decreasing lysosome's digestive function, and reflect decreasing in Phe hydroxylase and Tyr hydroxylase and reduction in NR4As pathway which cause reduction in oxytocin and in Nrf2 productive functions followed by reduction in VEGFa production, that will cause decreasing in myocardial function. Where, TNF-alpha down regulates expression VEGF receptors in human endothelial cells [22].

The Lysosomal dysfunction is associated with decreasing in mitochondrial function followed by increasing in both of cholesterol and TNFa production, where TNFa activate NLRP3 inflammasome pathway functions followed by enhancement the cardiovascular pathologies development.

That studies reported that: the Lysosomal dysfunction is associated with NLRP3 inflammasome activation [23]. And the TNf-a regulates transcription of NLRP3 inflammasome components and inflammatory molecules [24].

Also, the increasing in lysosomal dysfunction reflects decreasing in lysine followed by decreasing in GTPase and decreasing in mitochondrial function then followed by increasing in undigested polymers and increasing in TNF-α which enhanced the development of a number of cardiovascular diseases [25]. Also, Patients with acute myocardial infarction had statistically significant increased serum levels of PTEN & TNF-α gene activity [26].

So, it's clear that Patients with acute myocardial infarction are having severe Decreasing in both lysosomal and mitochondrial functions followed by increasing in the accumulated cholesterol, undigested polymers, and increasing in TNFa functional activities, which cause increasing in NLRP3 pathogenic functions which followed by reduction in oxytocin and in both of Nrf2 and VEGF-A production which cause reduction in endothelial function and increasing in the risk of CVD.

That both DPM and DBM are useful in acute cardiogenic circulatory collapse [27]. That previous study indicated that CVD characterized by severe reduction in dopamine and reduction in both of transport system and antioxidant function (due to reduction in Lys AAG and in Trp TGG) , that's why dopamine is useful for treating patients with CVD. Where , the Myocardial Infarction is a Consequence of Mitochondrial Dysfunction [28]. And, the inhibition in Trp will cause inhibition in mitochondria oxidative functions that cause PKU, ischemic damage, diabetes, pulmonary disease, and CVD, followed by inhibition in dopamine and in serotonin functional pathway, that it has been reported that : In classical PKU, the serotonin and dopamine biosynthesis are inhibited [29].

So, it's clear that both of CVD and PKU are characterized by severe reduction in dopamine , that means those two diseases are connected together in lysosomal dysfunction and mitochondrial dysfunction, mediated by reduction in Phe hydroxylase and in Tyr hydroxylase, and followed by increasing in the accumulated cholesterol, undigested polymers, which activate TNFa, that TNFa will activate NLRP3 pathogenic pathway, that mediated by reduction in oxytocin and in both of Nrf2 and in VEGFa function that will cause reduction in endothelial function and cause PKU, calcification and CVD.

Also, the Tumor Necrosis Factor-α (TNFa) promotes and exacerbates calcification in heart valve myofibroblast populations [30]. And , studies approved that the TNF-α antagonism is unlikely to be a beneficial therapeutic strategy in patients with acute myocardial infarction [31]. Also, the lysosomal dysfunction can Increase the concentrations of TNF-α which are found in acute and chronic inflammatory conditions [32].

Now, positively the Genetically-predicted TNF levels are associated with coronary artery disease and inversely associated with overall cancer [33]. While, Lysine Prevents Arterial Calcification in adenine-induced uremic rats [34].

So,, Lys "AAG" and Trp "TGG" prevent arterial Calcification by its role in activating both of lysosomal function and Mitochondrial oxidative functions that mediated by activating lysine acylation which promote RA synthesis, and activate Phe /hydroxylase and Tyr /hydroxylase which promote dopamine production and increase Antioxidant functions, and protect against PKU, diabetes, pulmonary disease, CVD, and protect against heart failure, that it has been reported that : Nuclear ATR lysine-tyrosylation protects against heart failure [35].

Also, the reduction in Trp will cause reduction in dopamine and in mitochondrial function that will cause reduction in transport system and cause cerebral ischemia, that it has been reported that cerebral ischemia due to extensive calcified vasculopathy, disruption of the basal ganglia-thalamo-cortical circuit, and nigrostriatal dopaminergic dysfunction are plausible pathogenic mechanisms [36].

So, lysine and Tryptophan are playing important role in Protecting against cerebral ischemia, Heart Failure, and also Prevents Arterial Calcification by enhancing lysosomal Functions and mitochondrial repairs and functions followed by enhancing estrogen production which prevent the accumulated cholesterol and un-digestive polymers [37].

Also , VEGF production regulated by angiotensin-2 is controlled by mitochondrial function, which regulated by intracellular ATPase and GTPase (produced by Lys and Trp) That studies approved that, mitochondrial function control delivery of nutrients and oxygen to tissues through the extension of blood vessels by angiogenesis [38].

So, decreasing in both Lys AAG and in Trp TGG will cause reduction in lysosomal function followed by reduction in mitochondrial function will increase all of cholesterol TNFa production and reduce angiotensin-2 and VEGF-A productive functions that can be the result of increasing the risk of cerebral ischemia, CVD, and Arterial Calcification, followed by reduction in neuro-protective effects on hypoxic motor neuro, and decreasing in the protection against memory impairment "Figure 1" "which Explains, and summarizes the basics of the importance of Lys and tryptophan in this work".

Also , the VEGF-A (where VEGFa is basically regulated by both Lys AAG and Trp TGG as discussed before) has a neuroprotective effect on hypoxic motor neurons, and is a modifier of ALS (amyotrophic lateral sclerosis) [39]. Also, it is important to note

that: VEGF A in serum protects against memory impairment in APP/PS1 transgenic mice by blocking neutrophil infiltration [40].

And, the protection of IL17 is activated by mitochondrial function, where IL17 is important activator to Glucocorticoids-beta synthesis via NR4As pathway (and prevent organs failure cholesterol accumulation), followed by activating B-arrestins and both of B-adrenergic and Nrf2 synthesis followed by activating angiotensin-2 (Ang2-AT2) and VEGF-A productive functions [41].

Also, both of Lys and Glu (Lys "AAG" is reversed copy of Glu "GAA") are having important role in stabilizing leucine "CTT" functional pathway and are important for activating mitochondrial function which regulate IL 17 production which activate NR4As pathway started by activating GC-beta, followed by activating angiotensin-2 and VEGF-A production, which reflect reduction in TNFa and in cholesterol.

So, Lysosomal dysfunction is associated with decreasing in mitochondria function and decreasing in VEGF-A followed by increasing in TNFa, where TNFa activate NLRP3 inflammasome pathway functions followed by activating the cardiovascular diseases, myocardial infarction as described in "Figure 1", (Figure 1 is explanation of main aspect of the importance of lysine & Trp in lysosome & Mitochondrial oxidative functional pathways)

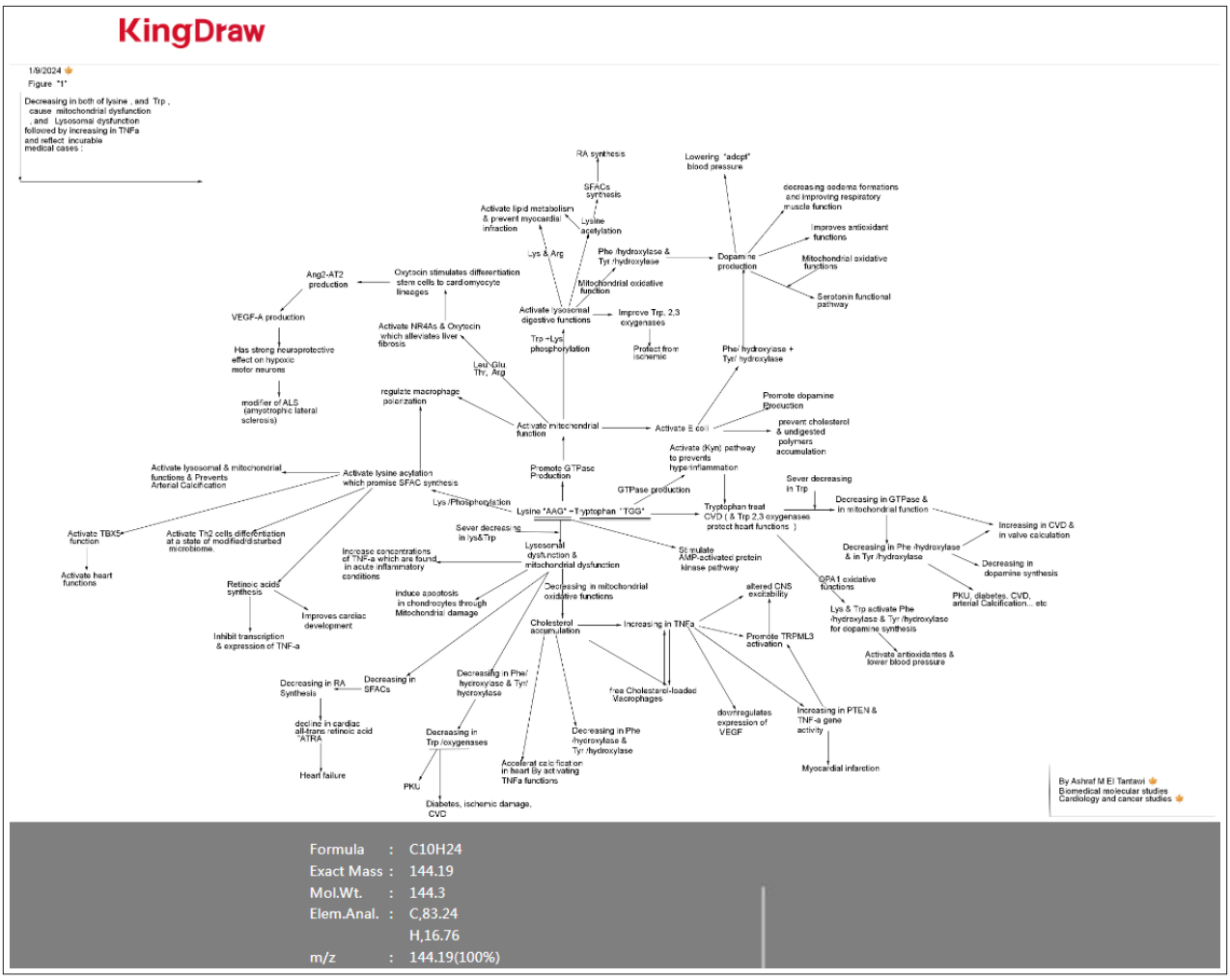

Figure 1

Both lysine and phenylalanine important for treating pulmonary disease, while Lys required for acylation & activating TBX5 : Firstly, pulmonary diseases characterized by mitochondrial dysfunction followed by increasing in cholesterol accumulation, and followed by defect in estrogen biosynthesis (where cholesterol is the substrate for estrogen synthesis regulated by synthase enzyme),followed by decreasing in IL17 and GC-beta production and decreasing in NR4As pathway, that it has been approved that Estrogen Inhibition Reverses Pulmonary Arterial Hypertension and Associated with Metabolic Defects [42].

Decreasing in Estrogen reflect increasing in cholesterol accumulation due to decreasing in OPA1 repair and functions, where mitochondrial repairs and functions activated by GTPase which produced by Trp "TGG "and by Lys "AAG ", that we can conclude : the Inhibition of estrogen Reflect Inhibition in mitochondrial functions that reflect sever decreasing in Lys "AAG" and in Trp "TGG" , that followed by Inhibition in dopamine production and reduction in the activation of NR4As pathway and followed by reduction or Inhibition in both of angiotensin-2 and VEGF-A production, followed by increasing in TNFa, and increasing in the risk of Pulmonary Arterial Hypertension, reduction in control delivery of nutrients and oxygen to tissues, memory impairment, and increasing in arterial calcification.

Also, we can conclude that sever reduction in both Lys "AAG" and Trp "TGG" cause lysosomal dysfunction and Mitochondrial dysfunction is the main for pulmonary disease "Figure 2", that it has been reported that mitochondrial dysfunction is a systemic phenomenon during chronic obstructive pulmonary disease COPD [43]. And, studies reported that Mitochondrial Dysfunction as a Pathogenic Mediator of Chronic Obstructive Pulmonary Disease and Idiopathic Pulmonary Fibrosis [44].

Also, the absence of Prolyl-4 Hydroxylase 2 (PHD2) indicate absence of A-Ketoglutaric acid which is a short-chain fatty acid, reflect sever decreasing in mitochondrial function and sever decreasing in both Lys and Trp, that cause pulmonary disease and cause other Incurable diseases as described in "Figure 2". That it has been approved: the Prolyl-4 Hydroxylase 2 (PHD2) Deficiency in Endothelial Cells Induces Obliterative Vascular Remodeling and Severe Pulmonary Arterial Hypertension.[45].

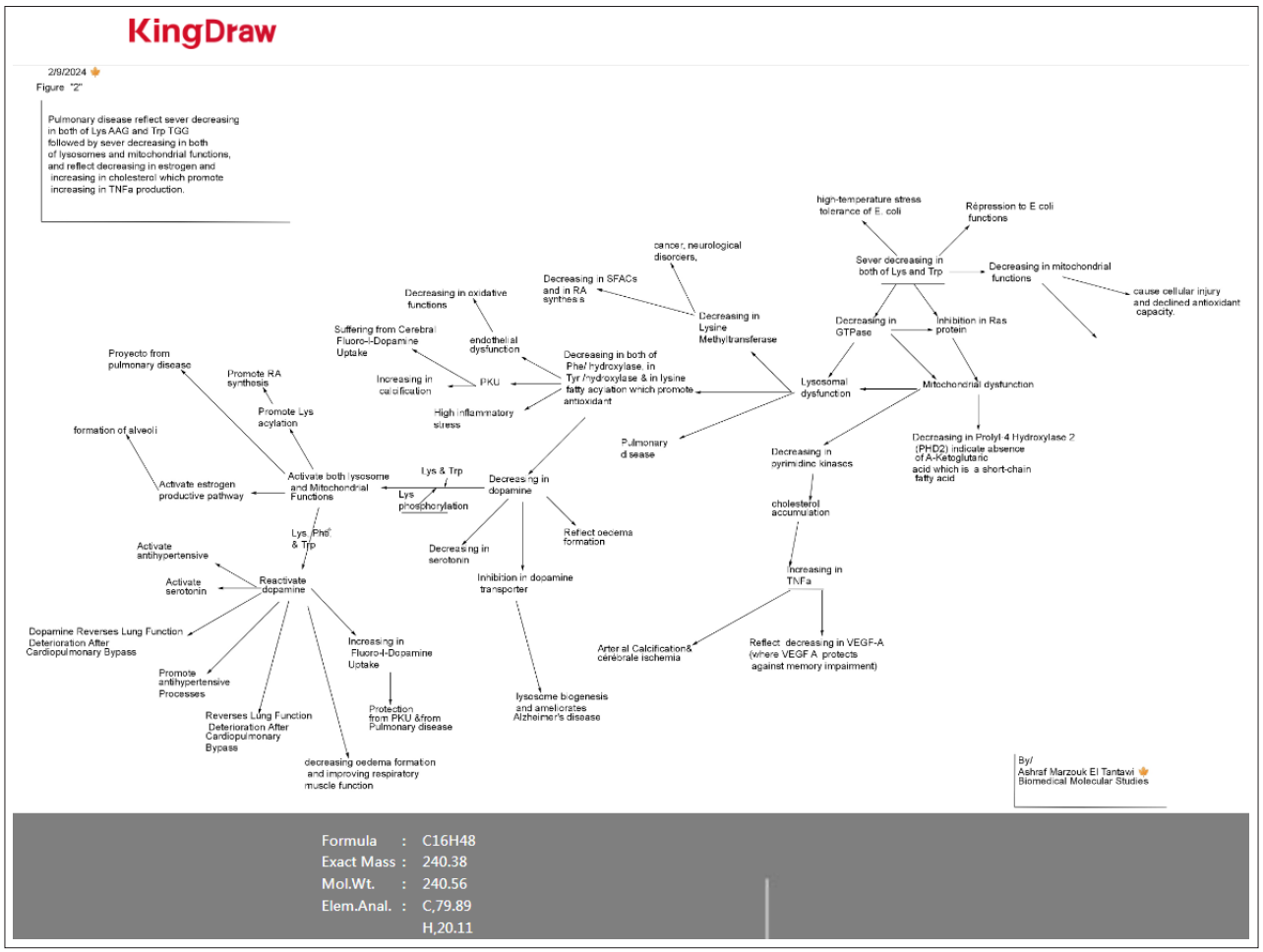

Figure 2

Also, studies indicated that: GTP-bound Rab7 promotes mitochondria–lysosome contact site formation and tethering, while mitochondrial TBC1D15 (Rab7-GAP) recruited to mitochondria via Fis1 drives lysosomal Rab7 GTP hydrolysis at mitochondria–lysosome contact sites [46]. So, pulmonary disease characterized by Inhibition in Ras proteins (which control mitochondrial function and control estrogen production) , followed by Inhibition in GTP bound Rab7, and followed by mitochondrial dysfunction that cause accumulation in cholesterol and increasing in TNFa functions as discribed in "Figure 2". Where other studies reported that, Ras proteins control mitochondrial biogenesis and function [47].

Also, Lysine acylation synthesis reflect Activation to Mitochondrial Aconitase in the Heart, mediated by activating ATPase and GTPase production, and followed by preventing the accumulation of cholesterol and protect from pulmonary disease [48].

Also, alterations in the expression of Lysine Methyltransferase have been linked to the genesis and progress of several diseases, including cancer, neurological disorders, and growing defects, [49].

So, the availability of lysine is necessary for lysine Acetylation synthesis mediated by Activating Mitochondrial Aconitase in the Heart through activating GTP-bound Rab7 which promotes mitochondrial and lysosome functions followed by preventing the cholesterol accumulation, and followed by activating Phe hydroxylase production which controls the phenylalanine metabolic functions, and followed by preventing aorta calcification "Figure 2".

Also, the absence of lysine will inhibit lysine fatty acylation followed by Inhibition to adipocyte B-adrenergic function which will be followed by decreasing in fatty metabolic process lead to cholesterol accumulation. That the presence of lysine is necessary to activate

the lysine fatty acylation of an anchoring protein mediates adipocyte adrenergic functions (which has the antioxidant function) [50].

Notice that Lys acylation is so necessary for activating short fatty acid chains "SFACs" production which necessary for activating retinoic acid production (which will be discussed later).

Also in the other hand, TBX5 is required for patterning of the cardiac system and maintenance of cardiomyocyte functions, where lysine is required for acetylation which required for activating TBX5 for Regulating heart development and function, "Figures 1&3" [51].

So, both of Lysine and Trp have so important roles in activating lysosomes and mitochondrial function which followed by activating Lysine fatty acylation which required for activating TBX5 function and antioxidant mediated by Phe /hydroxylase and Tyr/ hydroxylase productions which considered as stable mRNAs produced by E coli for modulation heart and brain functions, and necessary for controlling phenylalanine metabolic pathway.

I would like to give a little note that, arginine has important role in activating tRNAs and accelerate transport system pathway, that Arg is required to be included in mRNAs which produced by E coli to accelerate immune functional pathway that accelerate antioxidants and transport systematic pathway (which mainly regulated and promoted by GTPase production) function and prevent calcification and the accumulation of inflammation which can be the main for lysosomal and Mitochondrial disorders.

Also I would like to mention that presence of Arg is so important for accelerating transport system through activating tRNAs that prevent accumulated molecules and reduce calcification , that it has been approved that: L -Arginine prevents the over-expression of alkaline phosphatase (ALP, $p < 0.001$) and reduces matrix calcification ($p < 0.05$) in VICs treated with LPS [52].

And, Homo-arginine Supplementation Prevents Left Ventricular Dilatation and Preserves Systolic Function in a Model of Coronary Artery Disease [53].

And, decreasing in both of lysine and Trp will decrease mitochondrial oxidative function followed by decreasing in Lys acylation which followed by decreasing in TBX5 functional activities and decreasing in heart function and development, and also the decreasing in lysosome and Mitochondrial functions will be followed by increasing in inflammation and in cholesterol accumulation, and will cause decreasing in phe/hydroxylase production which cause increasing in the risk of both of PKU and the cardiovascular disease that it has been approved that: the cardiovascular phenotype of adult PKU patients is characterized by high levels of inflammatory and oxidative stress markers, endothelial dysfunction and vascular stiffness "Figure 2" [54].

Also, it has been approved that the abnormalities in patients with phenylketonuria consisted of widening and cupping of the metaphysis, an intact zone of provisional calcification [55]. And, The patient with malignant phenylketonuria (PKU) who underwent both CT and MR Imaging is reported, that CT demonstrated the characteristic calcifications of the basal ganglia [56].

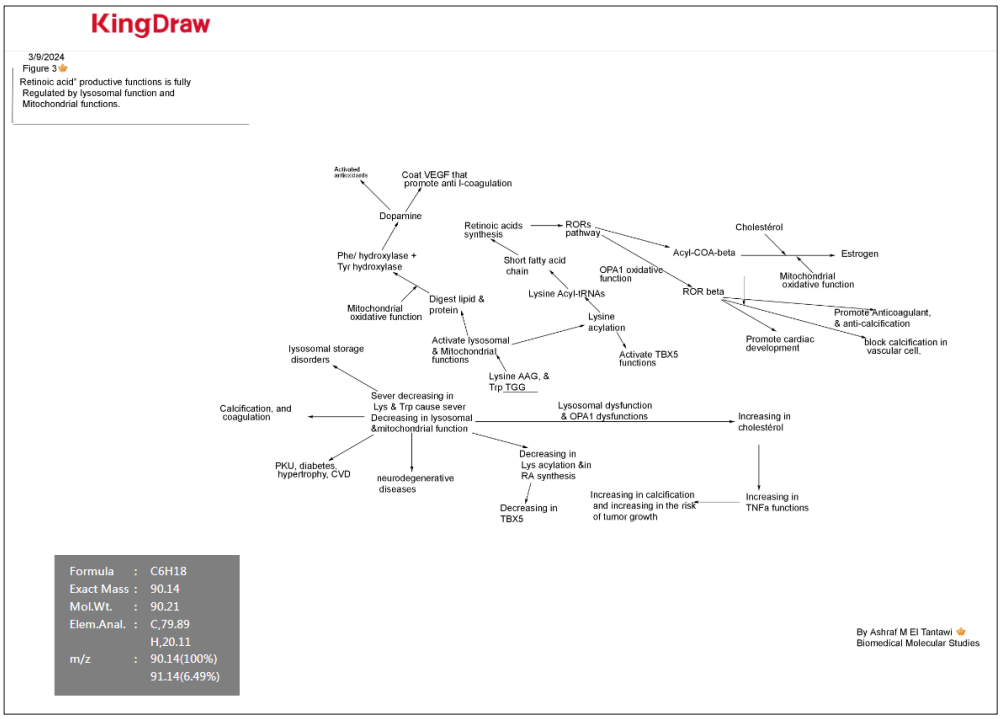

Figure 3

Also, decreasing in pyrimidine kinases (pyrimidine synthesis regulated by mitochondrial synthetase) reflect mitochondrial dysfunction, followed by increasing in cholesterol accumulation and decreasing in phenylalanine hydroxylase, which reflect reduction in

antioxidant function, which reflect reduction in estrogen synthesis and decreasing in dopamine synthesis, which followed by aorta classification and pulmonary disease.

Where, studies reported that: Deficiency in pyrimidine kinases cause cholesterol accumulation and increase the risk of coronary artery disease [57]. So, decreasing in Phe /hydroxylase reflect decreasing in both of lysine and Tryptophan followed by decreasing in lysosomes function which followed by decreasing in mitochondrial oxidative function that will be result in decreasing in both of Phe hydroxylase synthesis and in Lys acylation (which required for TBX5 function), and then the decreasing in lysosome and in mitochondria function will cause increasing in cholesterol and in TNFa which will be followed by increasing phenylalanine accumulation which will be followed by increasing in calcification and pulmonary disease "Figure 1 and 2".

Also, phenylalanine and Phe/hydroxylase controlled by lysine functions through translation and by activating mitochondrial functions, that will be the reason of protecting Against monocrotaline-induced pulmonary vascular remodeling and lung inflammation. Where studies indicated that 4-Chloro-DL-phenylalanine protects against monocrotaline-induced pulmonary vascular remodeling and lung inflammation [58].

So again, the lysine is basic controller to Phenylalanine and phe/hydroxylase. Functional pathway, that Lys stabilize Phe functions by translation process Lys "AAA, AAG"→Phe "TTT, TTC" where, both of lysine and Tryptophan TGG are the basic activator to mitochondrial repairs and oxidative functions, where Mitochondria necessary to activate all of Phe /hydroxylase, Tyr hydroxylase followed by dopamine productive functions.

Lysosomal dysfunction cause decreasing in mitochondria and in both of lysine Methylation and Phe /hydroxylase, where Lys and Trp required for alveoli and protect from pulmonary, and phenylketonuria. As we mentioned before lysine phosphorylation is the main activator for lysosomal function, where other studies approved that: the Loss of laat-1 transporter caused accumulation of lysine and arginine in enlarged, degradation-defective lysosomes [59].

And, lysine residues are required for phosphorylation of procathepsin L and are a common feature of the site on many lysosomal proteins [60]. That, as lysine decreased as so many of lysosomal protein will be decreased and cause lysosome damage.

So , as both of Lys "AAG" and Trp "TGG " decreased as mitochondrial oxidative functions will be decreased that will be the result of decreasing in Phe hydroxylase, Tyr hydroxylase, and Lys acylation that will cause reduction in both of RA and dopamine, and will cause reduction in antioxidant function where PKU characterized by sever decreasing in antioxidant function. That, oxidative stress is involved in the pathophysiology of the tissue damage found in PKU [61].

Also, decreasing in Phe /hydroxylase reflect decreasing in mitochondrial oxidative functions which demonstrate the energy deficit and oxidative stress which characterized PKU pathophysiology as described in "Figure 2" [62].

So I can conclude that the energy deficit and oxidative stress is related to decreasing in mitochondrial functions which originally related to decreasing in GTPase production which also related to decreasing in lysine" AAG" and in Trp "TGG" that finally cause decreasing in energy productive pathway, and cause increasing in oxidative stress or cause oxidative damage, where oxidative damage due to increasing in ATPase with sever decreasing in GTPase (which necessary for lysosomal and Mitochondrial functions), So, it's indicated to me oxidative damage due to increasing in "AAA" (which involved in heart failure and stroke), with sever reductions in "AAG" and sever reduction in TGG which finally characterized the PKU as the PKU is associated with sever reduction in energy production, sever reduction in dopamine production, sever reduction in lysosomal functions and sever reduction in mitochondrial oxidative functions which cause reduction in Phe /hydroxylase and reduction in Tyr / hydroxylase, followed by reduction in tryptophan-2,3-dioxygenase and in Lys acylation which cause reduction in RA production and finally caused the PKU, ischemic damage (due to decreasing in tryptophan-2,3-dioxygenase production which normally stabilized by proper lysosomal and mitochondrial function) and cause increase the risk of CVD, and increase the risk of pulmonary disease too.

And the Mitochondrial dysfunction cause cellular injury and declined antioxidant capacity as described in "Figures 2" [63]. Where, the mitochondrial redox homeostasis is a potential target for disease treatment, That disruption of mitochondrial redox homeostasis in muscle resulted in energy defect and exercise intolerance [64]. And, Mitochondrial necessary to activate antioxidant which the step toward disease treatment [65].

Also, Tryptophan "TGG" has the role of reducing the mRNA levels of proinflammatory cytokine genes and enhance mitochondrial function by increasing the mRNA levels of mitochondrial transcription [66]. While Dietary lysine levels modulate the lipid metabolism, mitochondrial biogenesis and immune response [67].

And, also it's very important to note that Lysine Acetylation has the roles of Activating Mitochondrial Aconitase in the Heart, which mediated by short fatty acid production which activate retinoic acid function that adopt heart function That Short-chain fatty acids activate acetyltransferase p300 [68,69]. Where, and lysine acyltransferases regulate protein synthesis, and are direct sensors and mediators of the cellular metabolic state [70].

And also, the short fatty acids (SCFAs) regulated by Lys acylation is important to promote retinoic acid productive functions, that SCFAs crosstalk with RARα in dendritic cells as a critical modulator that plays a core role in promoting Th2 cells differentiation at a state of modified/disturbed microbiome, "Figure 1 & 3" [71].

So, we can conclude that both of Lys and Trp are so necessary for activating mitochondrial oxidative functions which is so necessary to activate antioxidant function mediated by activating Phe/ hydroxylase, Tyr/ hydroxylase, and Lys acylation production which necessary to activate retinoic acid and dopamine, which has the role of activating antioxidant functions , where the PKU characterized by sever decreasing in antioxidant function and sever decreasing in Phe hydroxylase production "Figure 1".

The Lys acylation has the importance role in activating short fatty acid chains "SFACs" and acetyltransferase production which mediated the importance of proper metabolic pathways, where SFACs have important roles for activating retinoic acid functional pathway which has important role to activate antioxidant, that's why PKU characterized by reduction in Phe/ hydroxylase, (and

reduction in Tyr/ hydroxylase due to reduction in mitochondrial function), and reduction in acetyl transfers, and then reduction in SFACs production followed by reduction in both of retinoic acid function and reduction in dopamine productive functions.

Therefore, the lysine has an intense role in activating immune functions and anti-inflammatory processes, that the necessity of the Regulation of lysine methylation emerged as a critical regulator of neurological function and disease [72].

Again the meaning of the necessity of Lys methylation to be produced in vivo is reflecting the proper availability of lysosomal and mitochondrial function that reflect Phe/ hydroxylase productive pathway and Tyr/ hydroxylase pathway, and also reflecting the short fatty acid production which necessary for activating retinoic acid synthesis which necessary for activating RORs functional pathway and activating antioxidant function, which followed by activating NR4As pathway that enhance full controlling the antioxidant functions through producing oxytocin and Nrf2, and full angiotensin-2 and VEGF-A functional pathway which activate anti-inflammatory growth and processes to protect from many viral toxins and protect from many critical diseases including mitochondrial disorders and inflammatory disorders.

The Mitochondrial dysfunction and lysosomal dysfunction are reflecting reduction in lysine acylation and in Trp, which reflect decreasing in short fatty acids "SFACs" production which followed by reduction in RA (which regulated by Lys acylation & SFACs), and followed by increasing in cholesterol which activate increasing in TNFa that play important roles in inflammatory diseases, which characterized by swelling due to absence of lysosomal and Mitochondrial functions, where Some oncologists can be confused about swelling in tissue that can consider it as tumor cancer without understanding the basic of swelling.

Also, dopamine (regulated by Trp) may have beneficial effects on the respiratory system by decreasing oedema formation and improving respiratory muscle functions, "Figure 2" [73]. That Dopamine Reverses Lung Function Deterioration After Cardiopulmonary Bypass Without Affecting Gas Exchange [74].

So, The decreasing in both of lysine "AAG" and Tryptophan "TGG" cause decreasing in lysosomal function and in mitochondrial oxidative function, that will cause accumulation in the undigested polymers which cause lysosomal enlargement, then followed by decreasing in lysine acylation and in aminoacyl tRNAs, that will cause decreasing in Phe/ hydroxylase and decreasing in Tyr/ hydroxylase, followed by decreasing in retinoic acid "RA" and decreasing in dopamine productive functions, and followed by decreasing oedema formation and reduction in improving respiratory muscle functions, "Figures 1& 2".

Lysine and Tryptophan as discussed before are so important for activating mitochondrial oxidative function which necessary for both of pyrimidine kinases, and estrogen synthesis (which required for pulmonary alveolar functions). That it has been approved that, estrogen receptors, are required for the formation of a full complement of alveoli in female mice [75].

Now, we can understand why both of lysine and Tryptophan are so important for treating pulmonary disease, and treatment the increasing in Left vertical size , where the activated Lys phosphorylation roles and Tryptophan are reflecting the proper activating mitochondrial oxidative functions and lysosomal function that reflect reduction to the cholesterol and reduction to TNFa , mediated by activating both lysosomes and E coli functions, and followed by activating Lys acylation and Phe / hydroxylase productions.

Where studies approved that: the Aztreonam lysine "AZLI" (an inhaled lysine salt formulation) is effective, safe and well tolerated in the treatment of acute pulmonary exacerbations of CF. Superior improvements in lung function and quality of life suggest AZLI may represent a new treatment approach for acute pulmonary exacerbation [76].

And for sure the decreasing in lysosome and in mitochondria oxidative function will be followed by decreasing in phe / hydroxylase and in Tyr hydroxylase, then will be followed by accumulated Phenylalanine, and reduction in dopamine biosynthesis, which followed by decreasing in respiratory muscle functions "Figure 2". Also, the Inhibition in dopamine (due to Inhibition in both of Lys /hydroxylase and Phe /hydroxylase) is Associated with phenylketonuria and connected to lysosomal dysfunction.

Where, Phenylketonuria (PKU) is an autosomal recessive disorder caused by reduction in phenylalanine hydroxylase, which required for tyrosine hydroxylase synthesis, which is essential for dopamine production [77]. Also, adult Patients Suffering from Phenylketonuria are suffering from reduction in Cerebral Fluoro-l-Dopamine Uptake [78].

Where, the accumulation of phenylalanine in the blood of patients suffering from phenylketonuria, that are suffering from deficiency in both of lysine hydroxylase and Phenylalanine hydroxylase will be the cause of cause accumulation in phenylalanine followed by reduction in Tyr/ hydroxylase and reflect reduction in all of GTPase and mitochondrial function, that will cause reduction in dopamine synthesis (and reduction in antioxidant and in the formation of oedema formation and associated with reduction in respiratory muscle function), "Figure: 1& 2" [79].

So, sever decreasing in Lys and Trp will cause the lysosomal damage and mitochondrial dysfunction followed by the occurrence of such phenylketonuria (or the appearance of phenylketonuria)) which Associated with reduction in Phe/ hydroxylase and reduction in Tyr /hydroxylase (which considered as phenylketonuria) and associated with decreasing in dopamine, followed by increasing in the risk of pulmonary disease, and CVD.

Again, not only lysine is important to regulate mitochondrial oxidative functions, but also tryptophan which produce GTPase that promote mitochondrial oxidative functions, and also is important to promote dopamine production which is reported that Trp is necessary to regulates DA-ergic neurogenesis and Mitochondrial oxidative functions [80].

Both of lysine and Tryptophan are having important roles in activating mitochondrial oxidative function that enhance the Phe/hydroxylase and Tyr hydroxylase synthesis and prevent the accumulated phenylalanine and then control their proper metabolic pathway which necessary for protecting heart and brain proper function, and also are important for promoting IFNs production which will be discussed later.

Also, lysine acylation necessary for activating E coli, and allows the actual effects of lysine acetylation for protein productive

functions [81]. Also, as lysine necessary for activating lysosomal function, as dopamine also is very important for promoting lysosomal Functions and is strongly connected to lysine functions for promoting both of lysosomes and mitochondria function. Also studies reported that, Endothelial TRP channels are not only key players in physiological and pathological vascular functions thanks to their ability to sense a wide spectrum of chemical and physical stimuli. [82].

So, we can conclude that: both lysine phosphorylation and Tryptophan are connected together in their functions for activating lysosomal function and mitochondrial function, followed by activating Phe/ hydroxylase and Tyr/ hydroxylase production, then followed by their roles in activating E coli functions, and the necessity of Lys acylation in activating retinoic acid synthesis mediated by activating SFACs production "Figures 1&3".

Lysine, phenylalanine, and tryptophan, promote dopamine synthesis and Mitochondrial functions that protect from alzheimers disease. Firstly, as we discussed previously that both lysine and Tryptophan are having their strong roles in regulating all of lysosomes, mitochondria, and E coli functions, as sever decreasing in those amino acids can lead to sever decreasing in lysosomes and in E coli that will be the result of decreasing in heart function that led to ji Cardiac impairment.

That, patients suffer from a lack of aminoacyl tRNA productions and they suffer from lysosome and E coli dysfunctions [83]. Where previous study indicated decreasing in Lys will cause reduction in Lys acylation which will be followed by reduction in aminoacyl tRNAs synthesis and mainly cause reduction in lysosomal function which will be followed by increasing in accumulated undigested polymers and cholesterol and reduction in retinoic acids synthesis which regulated by SFACs which its production regulated by Lys acylation function.

And, the modulation of activating mitochondria and both of lysosomes and E coli can be a potential therapeutic strategy for age-associated cardiac impairment [84]. Also, Nuclear ATR lysine-tyrosylation protects against heart failure by activating DNA damage response [85].

And other studies approved that l-Lysine is an essential amino acid important for maintaining human health [86]. Now in the availability of proper mitochondrial function will control the Phenylalanine ratio through activating Phe hydroxylase production and will stimulate the increasing in immune antioxidant where Phe hydroxylase promote Tyr hydroxylase production which activate dopamine production (where dopamine considered as strong activator to antioxidant functional pathway), "Figure 5" [87].

Also it has been reported that : both of Phenylalanine (Phe) and tyrosine constitute the two initial steps in dopamine biosynthesis "Figure 1" [88]. Notice that, both of tryptophan and Tyr/ Hydroxylase Regulate Dopamine Synthesis, where studies have been approved that: the Tyr /hydroxylase (TH) catalyzes the rate-limiting step in the biosynthesis of dopamine (DA) and other catecholamines, and its dysfunction leads to DA deficiency and parkinsonisms [89,90].

Also, the Parkinson Diseases characterized by depletion of dopamine (which regulated by tryptophan, and by both of Phe/ hydroxylase and Tyr/ hydroxylase synthesis) [91]. Also, The Dopamine (productive pathway) has the role of increasing the force of contraction, and increase the elevation of the beating rate, and the constriction of the coronary arteries [92].

Whereas mentioned previously both of lysine and Tryptophan activate mitochondrial function that promote both of Phe/ hydroxylase and Tyr/ hydroxylase production which activate dopamine production "Figure 1&2", while mitochondrial synthase promote IL17 production which activate GC-beta, followed by activating B-adrenergic and both of Oxytocin and Nrf2 production which considered as strong antioxidant.

And now we can understand that the mechanism of dopamine is necessary for promoting antihypertensive pathway by lowering blood pressure. Where, the decreasing in Phe/ hydroxylase and in Tyr /hydroxylase will be associated with decreasing in dopamine and decreasing in antihypertensive pathway, "Figure 4&5". Where studies approved that: Dopamine considered as promoting antihypertensive pathway, by lowering blood pressure [93].

So Trp "TGG" which regulate dopamine productive functions is necessary to adjust antihypertensive pathway too .

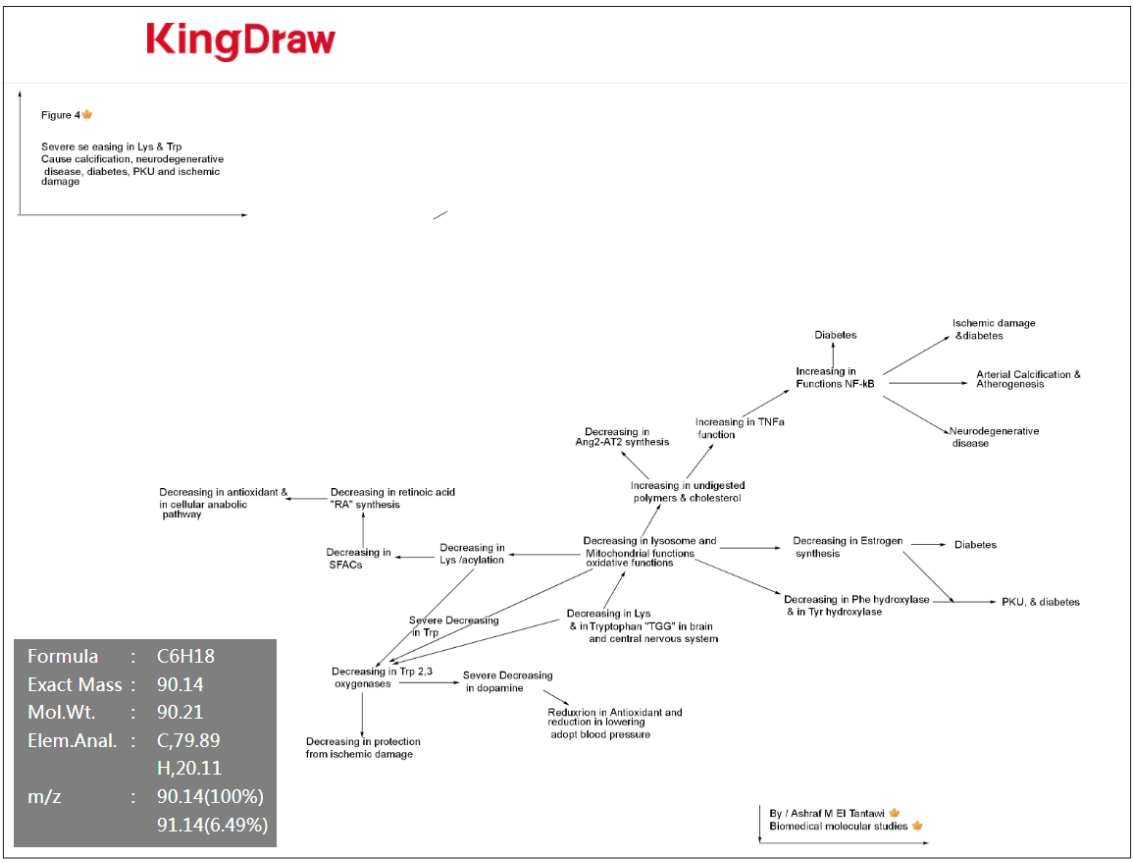

Figure 4

Where it has been approved that : Dopamine b: is considered as Important Antihypertensive Counterbalance Against Hypertensive Factors [94]. Where, the antihypertensive pathway mechanism is: the tryptophan and Lysine → activate mitochondrial repairs and functions → will activate Lys acylation ¬¬> activate methylation → which will activate Phe/ hydroxylase → followed by activating Tyr/ hydroxylase → followed by activating RA ¬¬> and activate dopamine →where dopamine synthesis in vivo is necessary to lowering "adopt" blood pressure "Figure 1& 4", also activating antihypertensive pathway reflect the activation to NR4As pathway mediated by activating the IL17 by mitochondrial synthase function → which activate GC-beta production → followed by activating both of Oxytocin and Nrf2 → Ang2-AT2 and VEGF-A productive functions → activate heme oxygenase →anti-inflammatory growth and processes.

Also, Tyr / /hydroxylase are found in heart tissue that indicated the necessity of dopamine in adopting heart functions directly and indirectly, that studies reported that: the activity of the enzyme Tyr /hydroxylase showed that was present in both hearts and in tissue with total sympathetic denervation [95].

So, dopamine (regulated by tryptophan, Phe/ hydroxylase, and Tyr/ hydroxylase) are having the role of protecting heart function and brain function through activating antioxidant function through enhancing "activating" mitochondrial function, followed by lowering "adopt" blood pressure Also it is reported that: L-lysine influences the selective brain activity in dependence on the biological significance of pain induced behavior [96].

So it is clear that lysine and Tryptophan are so important to cooperate together to improve lysosomal function followed by enhancing the activation of mitochondrial proper functions, followed by activating both of dopamine and increasing the proper antioxidant functions (by activating antihypertensive pathway) mediated by Improving both of Phe/hydroxylase and Tyr /hydroxylase y "Figure 1&4", followed by activating NR4As pathway, which mediated by activating IL17, that promote GCbeta and both of oxytocin and Nrf2 production which necessary for adopting antioxidant functions. Also it has been approved that : DA has direct autocrine effects on beta cells, and indirect paracrine effects through delta cells [97].

Where, deficiency in Phe/ hydroxylase will be followed by decreasing in both of antihypertensive pathway, and decreasing in Tyr/ hydroxylase will cause decreasing in all of lysosomal function and diseasing in mitochondrial function, and then decreasing in dopamine, which followed by Phe accumulation and increasing in Blood pressure and then cause decreasing in antioxidant function, that will be the result of causing PKU symptoms which is characterized by an accumulation of Phe and increasing in traditional cardiovascular risk, and associated with high levels of inflammatory and increasing in oxidative stress markers, increasing in endothelial dysfunction and vascular stiffness [98].

Decreasing in Retinoic acid related orphan "RORs" is fully connected to lysosomal dysfunction and mitochondrial dysfunction that reflect increasing in both of TNFa and cholesterol. There are strong cooperation between Lys, and Trp with RORs productive functions in activating immune functionality, that both Lys and Trp are very necessary for activating both of lysosomes functions and Mitochondrial oxidative functions which responsible for promoting RORs productive pathway that their functions reflect Inhibition to cholesterol accumulation and inhibition to TNF-a, followed by and activate both of IL17 and estrogen productions, that their proper functions reflect protection against PKU, pulmonary disease and against CVD.

And, I've mentioned previously that absence of lysine will inhibit lysosomal function and will inhibit lysine fatty acylation synthesis which necessary for SFACs production which by itself is necessary for Regulating retinoic acid productive functions, where the absence of lysine will be followed by Inhibition to adipocyte B-adrenergic function, which followed by decreasing in fatty metabolic process and increasing in both of undigested polymers and cholesterol accumulation, then cause decreasing in Retinoic acid functional pathway. That retinoic acid functional pathway is mainly connected with and regulated by lysosomal function and by mitochondrial function, that Mitochondrial functions is regulated by both lysine and Tryptophan functional pathways, where retinoic acid functions promote the decreasing and inhibition to TNFa functions "Figure 3".

That studies reported that: Retinoic acid receptor-related orphan receptor A (RORA) inhibits the transcription and expression of TNF, "Figure 1 & 3" [99]. So, it's very clear that Lys and Lys acylation are playing so important role in the decreasing and inhibition to TNFa through the role of Lys acylation in activating SFACs production which necessary for activating retinoic acid productive functions.

While, the short fatty acids "SFACs" production which promoted by lysosomal digestive functions and by mitochondrial oxidative function (and activate Lys acylation which important for SFACs production) are very important for retinoic acid synthesis, where in case of lysosomal dysfunction and Mitochondrial dysfunction will cause reduction in lipid metabolism and cause sever reduction in short chain fatty acids "SFAC". That it has been approved that "SCFAs" affect DCs by facilitating retinoic acid synthesis "Figure 1" [100].

Retinoic acid-related orphan receptors RORs (regulated by mitochondrial function) play a regulatory role in lipid/glucose homeostasis and various immune functions. That decreasing in Trp "TGG" and in Lys "AAG " will cause reduction in both of lysosomes and mitochondrial functions, and will be associated with increasing in cholesterol and in undigested polymers which promote the increasing in TNFa productive functions.

There is strong cooperation between Lys, Trp, and RORs productive functions in activating immune functionality, and in protecting against PKU, diabetes and calcification , that both of lysine "AAG" and Tryptophan "TGG " are having important role in the decreasing all of cholesterol, TNFa, and Calcifications, mediated by RA synthesis and mediated by activating antihypertensive pathway .

The Retinoic acid is necessary for Retinoic Acid Receptor-Related Orphan Receptors for running several cellular metabolic functions, that reduces apoptosis, reduces oxidative stress, evaluate cardiac development, and enhances the repair of infarcted myocardium, where the all-trans retinoic acid "ATRA" is having important role in dissolving Aorta calcification by promoting fission events throughout accelerating lysine and Trp functions for activating mitochondrial repairs and functions.

Where studies approved that: Retinoic acid (RA) established several functions during cardiac development, including actions in the fetal epicardium required for myocardial growth, (where retinoic acid reduce oxidative stress through enhancing antihypertensive processes), "Figure 1&3" [101].

And the activated acyclic retinoic acid pathway can reflect activated ribosomes and mitochondrial function for activating lysine acylation which necessary for activating SFACs production followed by activating Phe/ hydroxylase and Tyr/ hydroxylase production and IL 17 production from acting on IL2&6 (which means previous processes control the Dendritic cells function), followed by activating GCs-beta and both of oxytocin and Nrf2 which followed by activating angiotensin2 and VEGFa functional pathway that finally reflects protection against calcification .

Where studies approved that, acyclic retinoic acid pathway can specifically block calcification in a vascular cell [102]. I would like to mention that: it's clear the high level of endothelial dysfunction is the sign of mitochondrial dysfunctions, and reflect sever decreasing in lysine and Tryptophan and reflect increasing in cholesterol and decreasing in TNFa followed by failing to controlling to Dendritic Cells functions and then followed by increasing in vascular stiffness.

Also notice that, as both of lysosomes and mitochondrial dysfunction increased as the function of RORs will be decreased and will be associated with decreasing in antioxidant function and decreasing in lipid metabolic pathway that will be associated with decreasing in SFACs production, and will be followed by increasing in TNFa and increasing in the risk of high blood pressure and increasing in the risk of heart failure, that studies approved that: the proteomic analyses of human and guinea pig heart failure (HF) were consistent with a decline in resident cardiac all-trans retinoic acid "ATRA" "Figure 1" [103]. Also, the reduction In ROR pathway reflects Diabetic cardiomyopathy [104].

So, Reduction in RORs pathway reflect decreasing iny retinoic acid synthesis and then decreasing in Lys-acylation production which followed by decreasing in SFACs production and reduction in both of lysosomes and mitochondrial functions that reflect reduction in both of Lys "AAG"and Trp "TGG", followed by reduction in GTPase and reduction in RORs production (which regulated by RA synthesis and by OPA1 function), then followed by reduction in the estrogen production and increasing in the accumulated androgen, and Associated with accumulation in both of cholesterol and undigested polymers which promote the increasing in TNFa, which followed by increasing in NLRP3 inflamosomme pathogenic pathway, and associated with reduction in dopamine which followed by increasing in Blood pressure followed by increasing in calcifications, and cause Diabetic cardiomyopathy "Figure 3".

Where, studies approved that The Retinoic acid promote the increasing in the mRNA levels and protein synthesis of matrix Gla protein, and calcification inhibitory molecule, in human coronary artery and aortic valve cells [105]. The sever decreasing in Lys "AAG" and in Trp "TGG" promise decreasing in lysosomal Functions which play important role in atherogenesis, CVD and in coronary calcifications

The lysosomes are Membrane-bound organelles with roles in processes of degrading and recycling cellular waste, cellular signaling and energy metabolism. Sever decreasing in lysine and in tryptophan (decreasing in dopamine) cause lysosomal storage disorders, survival of tumor cancer, autoimmune disorders, blood disorders, Atherosclerosis, and neurodegenerative diseases. The lysosomal dysfunction promises the accumulated phenylalanine, where the absence of lys AAG reflect decreasing in the translations and stability of the normal Phenylalanine "TTC" functions that will cause Phe accumulation.

Also, sever decreasing in lysosomal functions cause decreasing in mitochondrial function that cause decreasing in lysine acylation and in SFACs production and followed by decreasing in retinoic acid synthesis and reduction in antioxidant pathway which followed by increasing in inflammation, and in cholesterol deposit in arteries walls that cause calcification.

As I discussed previously, both of lysine and Tryptophan are necessary for activating lysosomes and mitochondrial oxidative functions and both necessary for reducing inflammation, and cholesterol. Where, the Lys and Trp Protect against mitochondrial disorder and protect against PKU, pulmonary disease and CVD through activating lysosomes and OPA1 followed by activating Lys acylation which necessary to activate retinoic acid function mediated by producing SFACs , followed by activating both of RORs pathway and antioxidant function, that reflect inhibition or reduction to TNF-a.

"TRP" Channel Senses Lysosome Neutralization by Pathogens to Trigger Their Expulsion [106]. And, as we mentioned previously that Lys which activate lysosomal function is so necessary for translating and stabilizing Phe functions, that studies reported that: Involvement of lysosomes in substrate stabilization of tryptophan-2,3-dioxygenase [107].

And other studies indicated the necessity of Trp to protect against ischemic damage : that The tryptophan oxygenase are so necessary for protecting heart from ischemic damage, "Figure 1" [108]. So, lys is so necessary to promote and stabilize Phe functional stability which promote tryptophan dioxygenase which protect heart from ischemic damage "Figure 4".

And, it has been approved that: RAG-GTPases (which activated by Trp & Lys) and LAMTOR proteins are required for lysosomal leucine storage [109]. In other side, estrogen (regulated by mitochondrial functions) deficiency reflect diabetes and increasing in inflammations and cholesterol, followed by increasing in TNFa productive pathway, that studies reported that: Exacerbates Type 1 Diabetes-Induced Bone TNF-α Expression and Osteoporosis [110].

So severe Decreasing in both Lys and Trp will cause sever decreasing in lysosome and Mitochondrial functions followed by decreasing in SFACs production and increasing in cholesterol accumulation and decreasing in Trp 2,3- oxygenases production, which associated by increasing in TNFa that cause diabetes, coronary artery disease, ischemic damage, and atherogenesis.

The accumulated cholesterol is associated with undigested polymers due to lysosomal dysfunction lead to the deposit of cholesterol in blood vessels, calcification, and followed by increasing in TNFa synthesis "Figure 4".

That, deposition of cholesterol in the blood vessels in patients reflect decreasing in fat metabolism and decreasing in lysine acylation and in SFACs production that followed by increasing in TNFa production and increasing in coronary artery disease and atherogenesis.

That it has been reported that: The deposition of free cholesterol in the blood vessels in patients associated with coronary artery disease and atherogenesis [111].

So, the accumulated cholesterol in the blood vessels not due to deficiency in estrogen biostatistics but due to sever decreasing in lysine and in Tryptophan that cause lysosomal and Mitochondrial dysfunction and cause decreasing in lysine acylation and in both of SFACs and retinoic acid synthesis " Figure 3& 4". That it has been approved that: the lysosomal dysfunction has important role in atherogenesis [112].

Also, the disruption of Lysosome Function will cause decreasing functional pathway that will promote accumulation of undigested polymers and cholesterol that will be result of promoting NF-κB production and pathogenesis including phenylketonuria, neuro degenerative diseases, aorta calcification, and tumor survival [113]. Where, the Lysosome dysfunction cause neurodegenerative diseases [114]. Also, Lysosomes dysfunction contributes to the cardiovascular disorders which is known as lysosomal storage disorders [115].

So now, it's clear to me that lysosomal dysfunction is due to sever decreasing in both of Lys "AAG" and Trp "TGG" which contributes to mitochondrial dysfunction, then followed by decreasing SFACs and in RA synthesis, and followed by decreasing in Phe/ hydroxylase and in Tyr/ hydroxylase productive pathway, followed by decreasing in Trp 2, 3 oxygenases and associated with increasing in TNFa production That will cause PKU, the cardiovascular disorders, neurodegenerative diseases, coronary calcification, and atherogenesis "Figure 1&3".

And not only Lysine promotes the anticoagulant, antioxidant and activate NAADP, but also Trp "or dopamine" has same previous roles followed by anti-calcifications functions. also dopamine has important roles to activate VEGF for promoting anticoagulant function . Where studies approved that: the Tailoring of the dopamine coated surface with VEGF loaded heparin/ poly-L-lysine particles for anticoagulation" "Figure 5 & 6" [116].

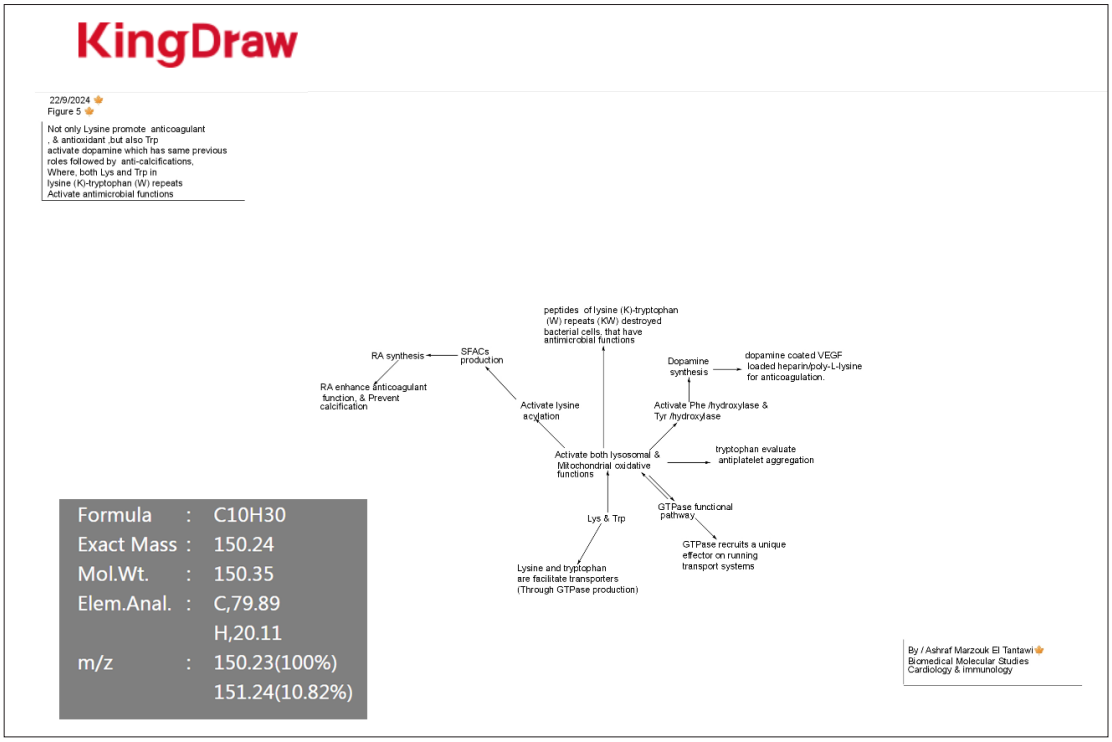

Figure 5

While, lysine promises the activation of Phe /hydroxylase, and Lys acylation (mediated by activating lysosomes and mitochondrial function) which necessary for RA synthesis, for activating antioxidant, and for increasing anticoagulant, that studies reported lysine promise strong cooperation with RA to enhance anticoagulant function, and to Prevent calcification "Figure 5" [117].

Also, Lysine-containing peptides can be used as promising antiplatelet drugs in prothrombotic conditions of the organism [118]. But in the other hand, the tryptophan derivatives evaluated for antiplatelet aggregation activity "Figure 5" [119]. So, it's clear that both of Lys and Trp are cooperating together for running anti-calcification and anti-coagulant functions, that both are so important for protecting heart functions and brain functions mediated by activating lysosomes and OPA1 oxidative functions followed by activating RA dopamine productive functions.

Both lysine and Tryptophan are necessary for transport system in neuron and in heart too: that Uniqueness of Tryptophan in the Transport System in the Brain and Peripheral Tissues [120]. And, both of Lysine and tryptophan are facilitative amino acid transporters through distinct sodium-independentsodium-independents "Figure 5" [121].

And, lysine, and tryptophan are possible modulators of growth, immune response, and disease resistance [122]. In the other hand, lysine and Trp considered as having the roles of activating antimicrobial functions through their role of activating both lysosomal digestive functions and Mitochondrial functions followed by activating both of RA and dopamine productive functions, and activating the proper transport functions, that it has been reported that: peptides composed of lysine (K)-tryptophan (W) repeats (KW) destroyed and agglutinated bacterial cells, demonstrating its potential as an antimicrobial agent "Figure 5"[123].

Also, Arg is Necessary to increase and cooperate with the Trp function through increasing transport system and facilitate tRNAs synthesis that prevent accumulated molecules, that studies approved that : L Arg and Trp may have distinct effects on the development of atherosclerosis [124]. The active transport is an energy-driven process, is activated by both of Lys and Trp functions through activating GTPase production, that each GTPase recruits a unique set of effectors on running transport systems, and those transitions help to define changes in the functionality of the membrane compartments with which they are associated using "Figure 5" [125].

So, both Lys and Trp facilitate the amino acid transporters across cells membranes through their role in activating GTPase production which activate Mitochondrial functions (and activate lysosomal digestive function) that activate antibacterial function and antiatherosclerosis, mediated by the role of GTPase in running the cellular transport functional pathways and activate anti-calcification pathway.

Pulmonary disease characterized by decreasing in tryptophan metabolic pathway:

We've discussed previously the lysosomal damage and mitochondrial dysfunction (due to sever decreasing in both of Lys and Trp) are connected to phenylketonuria and Associated with reduction in dopamine which followed by reduction in Phe/ hydroxylase and reduction in Tyr /hydroxylase, which associated with decreasing in mitochondrial function, and associated with decreasing in estrogen and followed by increasing in inflammation, that increase the risk of pulmonary disease, PKU, artery calcification and diabetes , (depending on the % of the decreasing in Lys and Trp).

Some studies approved that: DA have beneficial effects on the respiratory system by decreasing oedema formation and improving respiratory muscle function (only DA which regulated by lysosomal Functions and by Trp and also by proper mitochondrial function "not by TNFa" have beneficial effect on respiratory functions) [126].
I would like to note that decreasing in GTPase which produced by Trp TGG will cause reduction in Mitochondrial oxidative functions and reduction in all of Phe/ hydrolase, in Tyr/ hydroxylase, in oxygenases, and then reduction in dopamine production, that will be followed by reduction in transport system that will cause delays to cellular metabolic function , that will cause increasing in pathogenic survival and then progression in critical diseases pathways.

Also, Patients with inflammatory lung disease characterized by decreasing in tryptophan metabolic pathway, that Patients with acute exacerbations of COPD (AECOPD) have a unique metabolomic signature that includes a decrease in tryptophan levels [127].

Also, it has been reported that Hole hopping through tyrosine/tryptophan chains protects proteins from oxidative damage, "Figure 6" [128]. Also, Histidine-tryptophan-ketoglutarate solution decreases mortality and morbidity in high-risk patients with severe pulmonary arterial hypertension [129]. Where studies reported that the disruption of nocanonical functions of AARSs connects to various types of diseases [130].

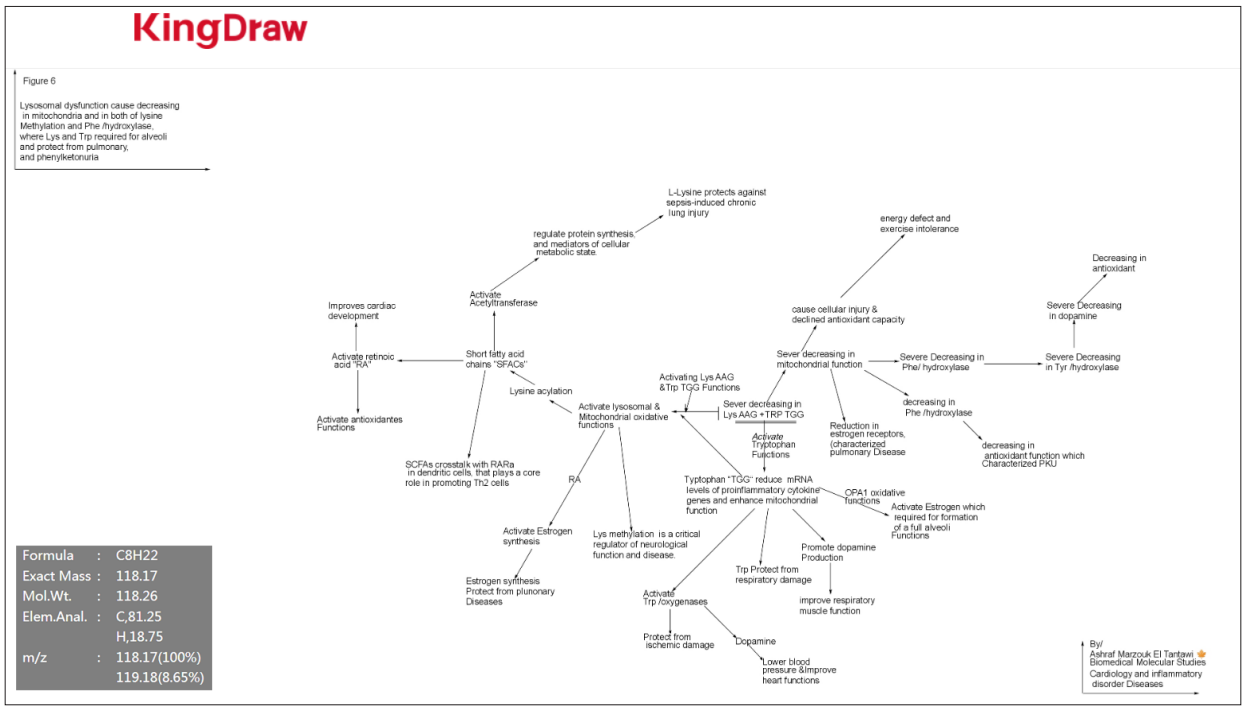

Figure 6

So, it's clear again that the sever decreasing in lysosomal Functions due to sever decreasing in lysine and in Trp (which protect against respiratory damages) that will be associated with sever decreasing in GTPase and decreasing in mitochondrial functions , followed by decreasing in Phe /hydroxylase and in Tyr /hydroxylase production, and followed by decreasing in transport system, and increasing in cholesterol and in inflammation, which associated with decreasing in dopamine synthesis and decreasing in the antioxidant functions and decreasing in estrogen (where decreased estrogen characterized the pulmonary diseases),"Figure 6", followed by increasing in the TNFa production and increasing risk of pulmonary disease, (depending on the % of the decreasing in Lys AAG and Trp "TGG").

Lys activate and protect lysosomal function that activate lysine acylation mediated lysosomal function and short fatty acid production, followed by improvement phospholipid functions.

Lysine has strong role in activating GTPase and ATPase production which activate lysine phosphorylation which necessary for lysosomal digestive functions, while GTPase activate mitochondrial function which activate all of lysine acetylation, Phe /hydroxylase which activate E coli functions, and activate Tyr/ hydroxylase followed by dopamine production.

Notice that, lysine AAG is the reversed copy of glutamate Glu "GAA", that are having same functions for activating lysosomal activation and activating antihypertensive pathway. While the deficiency in Lys AAG in vivo will revers deficiency in Glu GAA and consequently revers deficiency in the stability function of leu CTT and in Phe TTC, so positively the severe Decreasing in Phe/ hydroxylase productive functions reflect accumulation in leu "CCT" and in Phe "TTC" and reflect sever decreasing in Lys "AAG" and in Glu "GAA" that will be followed by coagulation, calcification, & decreasing in antimicrobial function.

Where, Lysine-selective molecular tweezers are cell penetrant and concentrate in lysosomes [131]. notice that both Lys & Trp are strong activator to transport system, that's why lysine is cell penetrant and concentrated in lysosome for activating Lys phosphorylation which promote lysosomal digestive functions, and Mitochondrial oxidative functions that protect against lung injury . And, L-Lysine protects against sepsis induced chronic lung injury [132].

So, as L lysine protect against sepsis induced lung injury, as all of Glu, Leu and Phe are having the same role in protecting from lung injury under availability of proper translation process, and are having the same roles in activating mitochondrial oxidative function and then promoting Phe /hydroxylase and Tyr /hydroxylase production which can indicated their necessity in promoting Lys acylation functions, and their necessity in protecting from PKU, from pulmonary disease, and from lysosomal disorders.

Lysine is so important to activate lysosomes digestive function and Mitochondrial functions followed by activating Lys acetylation which activate and increase the phospholipids transport, and activate Phe/ hydroxylase production (regulated by mitochondrial oxidative function) which has strong roles in activating both of Phe hydroxylase and Tyr/ hydroxylase productions which activate dopamine production, followed by activating Lys acylation which activate retinoic acid and reduce TNF-a production.

Where it has been reported that the synthesis of lysine fatty acylation (as I described before) will promotes lysosomal "digestion" targeting the TNF-α [133]. Also, TEADs are long-chain fatty acylated at Conserved lysine residues too [134]. So, Lys activate lysine acylation mediated by lysosomal oxidative function and short fatty acid production which necessary for retinoic acid productive functions and necessary for reducing TNFa, followed for protection against lung injury, and from PKU. Also, the necessity of lysine function has been indicated in this studies which reported LAAT-1 was required to reduce lysosomal cysteine levels and suppress lysosome enlargement [135].

Also, Lysine is a basic amino acid to activate transporte system (due to it encode Phe which connected with lysine for wide cellular effective functions) that is important on the vacuole membrane. Where the absence of lysine destabilizes purified Ypq1 and causes it to aggregate [136].

The Lysine also bind with phosphatidylinositol 3,5-bisphosphate for regulating trafficking and membrane dynamics by Direct Activation of Mucolipin Ca2+ Release Channels in the Endolysosome [137]. While, Trp residues of the JMD influence the electrostatic surface potential by controlling the position of neighboring lysine and arginine residues at the membrane–water interface [138]. That indicate the close interconnection between the functional stability of Lys and Phe in nature.

So, tryptophan is necessary to contribute lysine function and both are having important role in regulating membrane traffic and dynamic activities. It Is important to note that lysine-rich cluster necessary to activate the enzyme PtdIns(4,5)P2, to establish further interactions with diacylglycerol and/or acidic phospholipids (for increasing phospholipids transport), leading to the full activation of PKCα [139].

While, Trp chiral forms promote formation of hydrogen bonds and/or hydration in the PO2- moiety of phosphate group, That neutral and anionic lipid bilayers are sensitive to Trp [140]. So Trp necessary to activate phospholipid that form cell membrane and activate GTPase necessary for activating transport system, and necessary for activating Mitochondrial functions which activate lysine acylation which necessary for retinoic acid synthesis and for increasing fatty metabolism.

As we discussed before that increasing in TNFa will reflect decreasing in both of lysosomes and Mitochondrial functions and reflect decreasing in lysine acylation and in RA synthesis that reflect decreasing in Estrogen synthesis and decreasing in IL 17 synthesis that will be followed by decreasing in Gcbeta synthesis and reduction in NLR4 pathway which responsible for activating Nrf2 and angiotensin2 productive pathway. Some studies reported that Histone acetylation and chromatin conformation are regulated separately at the TNF-alpha promoter in monocytes [141].

Where, Oxidative stress and TNF-a induce histone Acetylation and NF-κB/AP-1 activation in Alveolar epithelial cells: Potential mechanism In gene transcription in lung inflammation [142]. And TNF-α regulates diabetic macrophage function through the histone acetyltransferase MOF [143].

While, Angiotensin II (which regulated by mitochondrial and regulate GC-beta and both of oxytocin and Nrf2) stimulates DNA and protein synthesis in vascular smooth muscle cells from human arteries [144]. That , the activated angiotensin-2 productive pathway reflect strong role in activating lysosomal functions and Mitochondrial oxidative functions and E coli activation that reflect reduction to TNFa and activation to DNA synthesis.

• That studies reported that: the angiotensin-2 has strong roles in activating DNA synthesis in organ culture [145]. So, we can conclude that Lysine and Tryptophan are necessary for activating lysosomes and mitochondrial functions followed by activating E coli which regulate DNA synthesis in tissues, mediated by activating anti-inflammatory growth and processes, and mediated by activating RA synthesis and activating all of Gc-beta Nrf2 and Angiotensin2 productive functions.

Also, it's reported that Phenylalanine (while Lys stabilize the Phe functional pathway) regulates the synthesis of α-amylase, trypsin and lipase through mRNA translation initiation factors – S6K1 and 4EBP1 [146]. And in other hand, the Trp58 plays a critical role in substrate binding and hydrolytic activity of human salivary alpha-amylase [147].

So both of Lys and Trp are necessary for stabilizing alpha amylase function, that the sever reduction in Lys and in Trp will reflect reduction in amylase functional stability and cause PKU and CVD, that we can conclude that PKU is characterized by reduction in dopamine and reduction in alpha amylase stability function.

TNFa can Only activate dopamine in case of lysosomal dysfunction followed by increasing in the risk of CAD. Firstly, we've discussed before that the activation Phe /hydroxylase is so necessary for activating Tyr hydroxylase production which is so required for dopamine synthesis, while Phe /hydroxylase synthesis is stabilized by Lys functions associated with proper lysosomal function, and stabilized Mitochondrial oxidative functions, where dopamine has antioxidant function.

Also it has been reported that: Tumor necrosis factor-α modulates GABAergic and dopaminergic neurons [148]. And the same time, the Systemic tumor necrosis factor-alpha decreases brain stimulation reward and increases metabolites of serotonin and dopamine [149]. Where TNFa which activated by undigested polymers and cholesterol (in lysosomal dysfunction) can activate the mutated dopamine which cannot promote brain function and antioxidant.

And the higher free dopamine levels (in case of lysosomal dysfunction and OPA1 dysfunction that cause mutated or up normal dopamine molecular structure) are an independent risk factor for future coronary events in CAD patients [150]. Where, Lysine fatty acylation promotes lysosomal targeting of TNF-α [151]. And Lys decreases mRNA and TNF-α protein in IL-1β-stimulated chondrocytes [152].

So, lysosomal dysfunction (due to the sever decreasing in Lys phosphorylation and sever decreasing in both of Trp and Glu amino a. functions that Glu "GAA" is the reversed copy of Lys "AAG") will cause accumulation of undigested polymers and cholesterol, which by itself promote the increasing in TNFa which can confuse us through considering that TNFa is promoting dopamine synthesis (but TNFa can promote mutated dopamine) followed by the increasing in the risk of coronary artery disease. The dopamine which promoted by TNFa can promise its mutated molecular structure which will not activate antioxidant function and may can promote mutated serotonin, that can increase the risk of coronary artery disease.

Notice, the lysosomal dysfunction cause accumulation of TNFa which promote CAD which connected by hypotension due to decreasing in ATPase and GTPase. That, Hypotension associated with patients with coronary disease [153,154]. While, Lys can treat CVD and hypotension, that Prevents Arterial Calcification in Adenine-Induced Uremic Rats [155].

Notice that: the availability of Lys AAA with decreasing in Lys AAG and Trp TGG will be the result of decreasing in GTPase, followed by decreasing in activating Mitochondrial oxidative functions, that will cause increasing in cholesterol accumulation and decreasing in both of IL17 and estrogen productive functions, that will increase the CVD risk and T2D,that studies reported That: association of 2-AAA with future risk of T2D. And association of lysine with subsequent CVD risk [156].

So both of Trp TGG and the Lys triplet AAG as we discussed previously are so important for activating GTPase (and transport system) and activating both of mitochondrial and lysosomal digestive functions followed by preventing the cholesterol accumulation (through activating Lys acylation which activate SFACs and followed by activating retinoic acid productive function), and then activate both of IL17 and GC-beta production followed by oxytocin and Nrf2 production through controlling dendritic cells functions.

Also it's very important to note that the proper functions of dopamine is in the availability of lysosomal proper Functions, and when regulated by Phe/ hydroxylase which necessary for Tyr/ hydroxylase production which promote dopamine production (but in availability of lysosomal dysfunction the dopamine will not adopt heart and brain function and will be replayed by TNFa production function which activated by cholesterol), where Dopamine increased pulse pressure, heart rate and circulating epinephrine € and norepinephrine (NE) levels [157]. Also, It has been approved that dopamine improve depressed myocardial function following acute coronary arterial embolization, at least temporarily [158].

Dopamine which promoted by both of Phe/ hydroxylase and Tyr/ hydroxylase increase antioxidants function due to the No of hydroxylase groups in phenolic rings which originally formed from Phe/ hydroxylase and Tyr/ hydroxylase. Where it has been reported that Dopamine has stronger antioxidant activity than other related compounds that is correlated to the numbers of hydroxy groups on the phenolic ring [159].

Notice Brain Disorders Due to Lysosomal Dysfunction (which reflect reduction in lysine acetylation and in both Phe/ hydroxylase and Tyr/ hydroxylase) [160]. But, in case of lysosomal dysfunction (sever decreasing in Lys AAG), the TNf-a will improve dopamine synthesis which can be associated with CVD and heart failure. Where studies reported that Cardiac dopamine D1 receptor triggers ventricular arrhythmia in chronic heart failure [161].

Lysosomal dysfunction Cause LV hypertrophy and cardiomyopathy mediated by mitochondrial dysfunction, and increasing in TNFa. Firstly, it has been summarized that: the effects of anti-TNF-α treatment in patients with and without heart disease and describes the involvement of TNF-α signaling in a number of animal models of cardiovascular diseases [162]. Also, TNF-α blockade may improve insulin resistance and lipid profiles in patients with chronic inflammatory diseases [163].

Where, the TNf-a is increased upon the lysosomal dysfunction and then upon the increasing in cholesterol, that it has been approved that: the free Cholesterol-loaded Macrophages are an Abundant Source of Tumor Necrosis Factor [164]. And the accumulation of cholesterol and pro-inflammation in myocardium will be subject to heart failure [165].

So, the lysosomal dysfunction is Abundant Source of the accumulation of undigested polymers and cholesterol which are the Abundant Source of TNFa, and consequently are the Abundant Source of not normal macrophages and then are the basic source of calcification, CVD and heart failure.

Decreasing in GTPase cause mitochondrial dysfunction and increase the risk of of heart failure mediated by decreasing in lysosomal function and increasing in TNFa functions, where the decreasing in lysine and tryptophan reflect reduction in GTPase and increasing in hypertension, that studies approved that: L tryptophan promise as a naturally occurring antihypertensive compound [166].

So, the cardiomyopathy caused due to lysosomal dysfunction (which subject to sever decreasing in Lys AAG andmeans in Trp) followed by mitochondrial dysfunction, and followed by decreasing in both ATPase and GTPase, followed by decreasing

in mitochondrial oxidative function and in Phe hydroxylase production, then associated with accumulation in cholesterol and in undigested polymers which subject to activate TNFa followed by decreasing in both of angiotensin-2 and VEGF-A, that will increase the improper proliferation in vertical tissue cells and cause increasing in LV hypertrophy.

Positively, Lysine with this triplet "AAG" is the most effective amino acid for activating lysosomes digestive functions and Mitochondrial repairs and functions (where it has been reported previously that AAA is associated with heart failure), where ATPase, and GTPase produced by Lys (and by Trp) are necessary for activating lysine Phosphorylation for promoting lysosome digestive functions, followed by activating mitochondria and E coli functions followed by activating Phe/ hydroxylase and Tyr /hydroxylase production, while Trp "TGG" is so necessary for promoting mitochondrial oxidative function (through activating GTPase production) and necessary for activating dopamine production.

Both of Lysine "AAG" and tryptophan "TGG" adopt hypertension, and activate antioxidant, followed by activating the protection from Type-2 Diabetes. That , Treatment with L-lysine seems to slow down the progression of diabetic nephropathy [167]. And, phenylketonuria (which characterized by lysosomal dysfunction and Mitochondrial dysfunction, as discussed before) associated with diabetes disease too [168].

So we can conclude that PKU associated with reduction in both of dopamine and alpha amylase and also associated with calcification and diabetes.

So, treatment with lysine and Trp in proper arranged molecular structure will reduce diabetes and phenylketonuria syndrome mediated by activating both of lysosomes and mitochondrial functions followed by activating E coli function and followed by activating nrf2, Angiotensin2 and dopamine productive pathways.

Where, Tryptophan Predicts the Risk of diabetes through reacting Mitochondrial oxidative function and reactivate proper transport system and so will promote the Phe hydroxylase and Tyr hydroxylase production regulated by Mitochondrial oxidative functions, and then reactivate dopamine which considered as antioxidant. Where, studies reported that: Tryptophan Predicts the Risk for Future Type 2 Diabetes [169].

The decreased Trp reflect decreased GTPase and reduction in lysosome and Mitochondrial oxidative function, that reflect reduction in transport system pathway which will delay transport of amino acids and delay cellular metabolic pathway which will promote the accumulation of molecules.

In general, we can conclude that: lysosomal dysfunction reflect decreasing in Trp (and decreasing in dopamine synthesis in vivo), that associated with decreasing in ATPase followed by decreasing in GTPase, and followed by decreasing in both of mitochondrial OPA1 oxidative functions, and then consequently followed by reduction in Phe/ hydroxylase (phenylketonuria), and followed by accumulation in Phenylalanine which Associated with calcification in blood vessels (where calcifications due to accumulation of both of undigested polymer and cholesterol).

And there is another study approved the Potency of Lys functions that it activate lipid metabolism that prevent lipid and cholesterol accumulation (not inhibiting lipid metabolis) that activate antioxidant function through promoting lipid digestion and promoting lysine acylation ND enhancing SFACs production which enhance retinoic acid synthesis and activate antioxidant functions.

Where study reported that: Lysine is an Lp(a)-binding inhibitor acts as antioxidant, that Lysine harvesting is an antioxidant strategy and triggers under ground polyamine metabolism]. And, Where, Treatment with L-lysine seems to slow down the progression of diabetic nephropathy. And, L-Tryptophan Suppresses Rise in Blood Glucose and Preserves Insulin Secretion in Type-2 Diabetes.

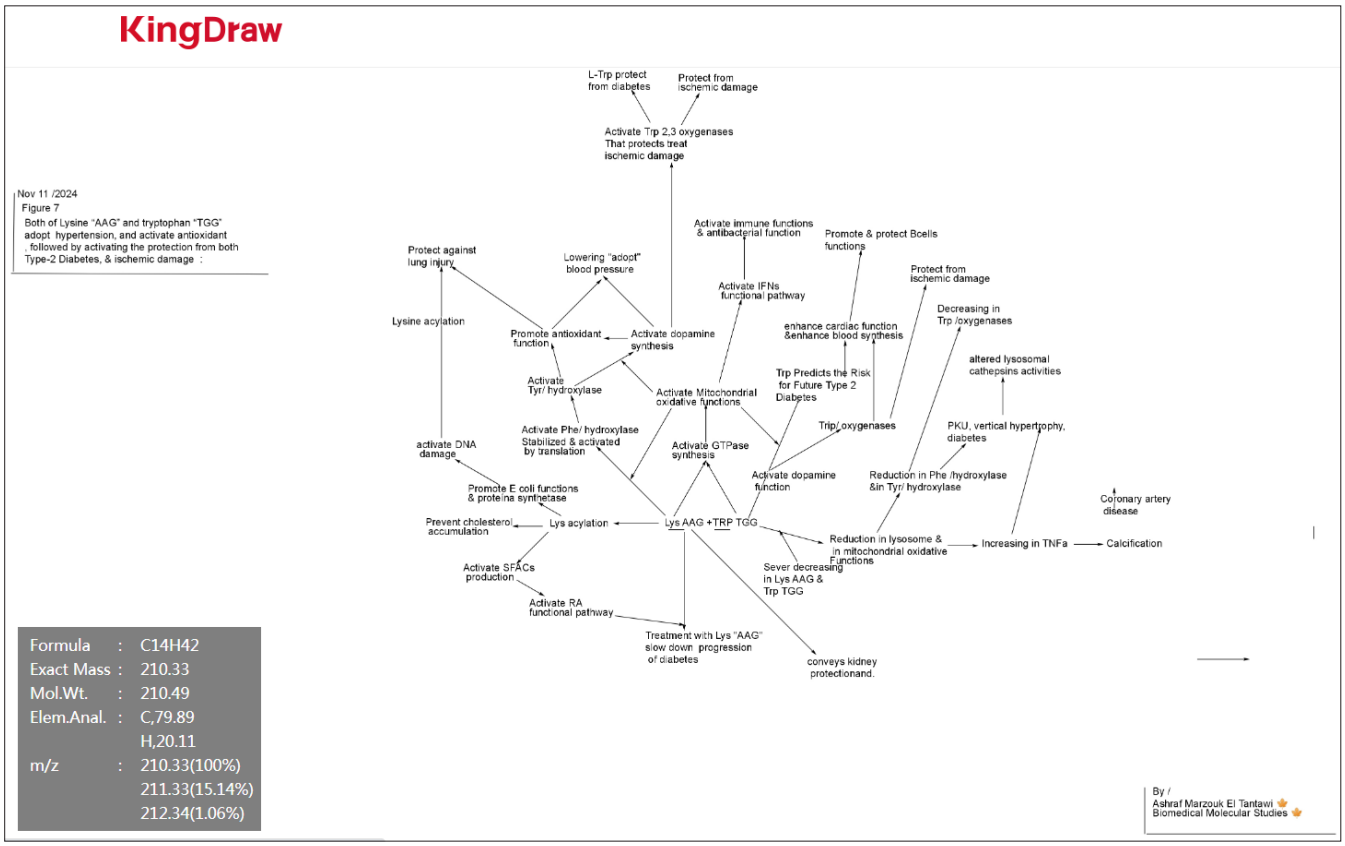

Figure 7

So, both Lys and Trp are having the Potency to activate lysosomes and Mitochondrial oxidative functions which activate lipid and protein digestion and enhance Phe hydroxylase and Tyr hydroxylase followed by activating lysine acylation which activate SFACs production and promote the RA synthesis and enhance antioxidant functions followed by dopamine synthesis and protection from ischemic damage and from both of diabetes and PKU.

Conclusion

Phenylketonuria characterized by severe Decreasing in GTPase and severe Decreasing in both lysosomal function and in mitochondrial functions which due to severe Decreasing in both Lys and Trp, and associated with high accumulated undigested polymers and cholesterol, (which activate TNFa pathogenic function), and characterized decreasing in antioxidants, followed by decreasing in both of Phe /hydroxylase and Tyr/ hydroxylase and followed by decreasing in both of lysine acylation and in dopamine. Reduction in Trp "TGG " and in Lys "AAG" cause decreasing in oxygen species and in estrogen Synthesis (mediated by decreasing in Mitochondrial oxidative function), followed by accumulation in androgen and in pro-inflammation including cholesterol which activate the increasing in TNFa functional pathways which activate pathogenic pathways.

I can conclude that PKU characterized by sever decreasing in Phe hydroxylase and sever decreasing in both alpha amylase and dopamine functional stability, and also characterized by calcification and diabetes.

-Lysosomes as important native tools for controlling B cells function through activating dendritic cells for activating Anti-Tumors, and for activating myocardial protection, that Lys phosphorylation and Trp are having strong roles in activating all of lysosomal function, Mitochondrial oxidative function and E coli functions.

Severe Decreasing in both Lys and Trp will cause sever decreasing in lysosome and Mitochondrial functions followed by cholesterol accumulation and decreasing in Trp oxygenases production, which followed by increasing in TNFa that will cause PKU, diabetes, coronary artery disease, ischemic damage, and atherogenesis.

Both Lys and Trp facilitate the Transport System across cells membranes via activating GTPase which activate antibacterial function via activating mitochondrial oxidative functions followed by activating Lys acylation which necessary for activating retinoic acid, which activate antioxidant, antiatherosclerosis, and anti-calcification, that protect from pulmonary disease and from CVD.

The lysosomal dysfunction is Abundant Source of the accumulation of undigested polymers and cholesterol which are the Abundant Source of the increasing in TNFa, and increasing in the abnormal macrophages, and then the lysosomal damage is the main for Mitochondrial damage and the main reason for the increasing in calcification, followed by CVD, and heart failure.

The treatment with lysine and Trp will protect against phenylketonuria syndrome mediated by activating both of lysosomes and mitochondrial functions followed by activating Phe /hydroxylase, Tyr /hydroxylase and lysine acylation which activate retinoic acid functions, followed by activating Nrf2, Angiotensin2 and dopamine productive pathways.

The lysosomal dysfunction promises accumulated phenylalanine, inflammation, and cholesterol deposit in arteries walls and exert calcification due to Mitochondrial dysfunctions (which activated by Lys and Trp), followed by increasing in TNFa production al pathway which activate pathogenic pathways.

The lysosomal dysfunction cause accumulation in the undigested inflammation, polymers, and in the accumulation of cholesterol. Lysosome dysfunction contributes to cardiovascular disorders, neurodegenerativee diseases, coronary calcification, and atherogenesisMitochondrial disorder through severe Decreasing in Lys AAG and Trp TGG.

Lysine "AAG" has strong role in activating ATPase production which activate lysine phosphorylation in lysosomes, and activate lysine acylation which activate short fatty acid chains which are very necessary for activating retinoic acid functional pathway in vivo which activate antioxidants functions and necessary for activation brain and heart function. Lys and Trp activate Phe hydroxylase which activate E coli functions, followed by activating Tyr/ hydroxylase and dopamine production.

Lysine AAA, AAG, ←necessary to encode and stabilize the Phe TTT, TTC functions, where the lysine AAG is the reversed copy of glutamate Glu "GAA", that are having same functions for activating lysosomes and activating antihypertensive pathway (as discussed before) and both promise the stability of leucine "CTT" functional pathway.

Lysine and Trp are having important roles in activating GTPase which control lysosome function and control both of Mitochondrial functions in heart, and control Dendritic cell function, where GTPase is so important to control the mitochondrial functions which regulate MHC Class II Presentation (which produced by B cells), that contribute to myocardial protection via activating antihypertensive pathway and NR4As pathway.

Lysine has important role for activating Glu, and leucine and activate GTPase production which necessary for mitochondrial Biogenesis mediated by lysine acylation production which necessary for activating retinoic acid and heart functions.

The absence of lysine AAG and in Trp TGG will cause dysfunction in both of lysosomes and Mitochondrial oxidative functions, followed by decreasing in Phe/ hydroxylase production, and decreasing in lysine acylation which cause decreasing in RA and decreasing in both of antioxidants and decreasing in alpha amylase, that followed by increasing in the accumulation of phenylalanine, and accumulation in both of un-digestive polymers and cholesterol that cause phenylketonuria associated with diabetes and Calcifications.

Also, we can conclude that both of Lys "AAG" and Trp "TGG " are so necessary for activating mitochondrial oxidative functions which is so necessary for activating antioxidant functions, which promote Phe/ hydroxylase & Tyr/ hydroxylase production and activate lysine acylation which is so important for activating retinoic acid, where the PKU characterized by sever decreasing in antioxidant function and sever decreasing in Phe/ hydroxylase production.

Also Lys acylation has the importance role in activating short fatty acid chains "SFACs" and acetyltransferase production which mediated the importance for activating retinoic acid functional pathway, that's why PKU characterized by reduction in Phe/ hydroxylase, (and so reduction in Tyr/ hydroxylase due to the reduction in mitochondrial oxidative function).

Both Lys AAG and Trp TGG are having strong roles to adopt lowering blood through activating Phe hydroxylase, Tyr hydroxylase, and dopamine (which characterized by lowering high blood pressure), and having strong roles in protecting against PKU, diabetes, CAD, pulmonary disease and against both of calcification and CVD.

So I can conclude that the energy deficit and oxidative stress is related to decreasing in mitochondrial functions which originally related to decreasing in GTPase production which also related to decreasing in lysine" AAG" and in Trp "TGG" that finally cause decreasing in energy productive pathway, and cause increasing in oxidative stress or cause oxidative damage, where oxidative damage due to increasing in ATPase with sever decreasing in GTPase (which necessary for lysosomal and Mitochondrial functions), So, it's indicated to me oxidative damage due to increasing in "AAA" (which involved in heart failure and stroke), with sever reductions in "AAG" and sever reduction in TGG which finally characterized the PKU as the PKU is associated with sever reduction in energy production, sever reduction in dopamine production, sever reduction in lysosomal functions and sever reduction in mitochondrial oxidative functions which cause reduction in Phe /hydroxylase and reduction in Tyr/hydroxylase, followed by reduction in tryptophan-2,3-dioxygenase and in Lys acylation which cause reduction in RA production and finally caused the PKU, ischemic damage (due to decreasing in tryptophan-2,3-dioxygenase production which normally stabilized by proper lysosomal and mitochondrial function) and cause increase the risk of CVD, and increase the risk of pulmonary disease too

Conflict of Interest

I'm Ashraf M El Tantawi is the only one author that studied and wrote this work. And I am the only author declare that the research was conducted in the absence of any commercial or financial relationships "which could be construed as a potential conflict of interest".

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