

Decreasing in Lysine Reflect Lysosomal Dysfunction and Accumulated Phenylalanine which Connected to WMH and CVD and Both of Phenylketonuria and Calcifications where N-Acetylcysteine Prevent Organs Failure

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1. High Lights

_Lysine and lysine acylation are so important for both Phe and E coli functions for improving own necessary mRNAs production and improve protein synthesis which include dopamine synthesis (regulated by Tyr functions too).

_Lysine is the basis of lysine acylation (which formed upon ATPase effective function which regulated by lysine "AAG AAA") important for aminoacyl-tRNAs production which regulate phenylalanine /hydroxylase, and E coli functions necessary for mRNAs production and dopamine synthesis, that necessary for running antioxidant functions (mediated by activating NR4As pathway), and necessary to prevent both of WMH, aorta calcification, and CVD.

_Lysine activate lysosome functions through promoting ATPase which activate lysine phosphorylation on lysosomal surface, and GTPase which promote mitochondrial fusion and repair, followed by activating lysine acetylation and Phe/ hydroxylase which responsible for activating E coli, protein synthesis, and dopamine mediated by Tyr hydroxylase production.

_Nuclear ATR lysine-tyrosylation protects against Heart failure by activating DNA damage response (mediated by activating Phe H synthesis and E coli activation by activating lysine acetylation, and Phe/ hydroxylase followed by mRNAs production and dopamine production).

That, the RNA (produced by E coli) is 2'-O-methylated and

demonstrated higher stability that can and will improve immune for high anti-inflammatory processes stability and so will improve heart impact functions.

_ Phenylalanine activate mitochondria through activating RhoA/Rho-associated kinase pathway (which activated by lysine), indicating that Phe is completely connected to lysine "AAA, AAG" functions where Lys necessary for activating ATPase, and RhoA/Rho-associated kinase pathway.

_ phenylketonuria due to sever decreasing in lysine "AAA, AAG" function followed by lysosomal dysfunction and deficiency In both of ATPase and in Lys acetylation production, which followed by decreasing in Phe/ hydroxylase, and reduction in dopamine production..

2. Figures of this work:

1.

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3. Abstract

Phenylalanine function stabilized by lysine which found on lysosomal surface, that Phe necessary to regulate the synthesis or secretion of α -amylase, trypsin and lipase, where the Severe acute pancreatitis in a child with phenylketonuria.

The phenylketonuria due to decreased lysine followed by lysosomal dysfunction that will be result of deficiency in phenylalanine function that will not form pancreatic enzymes and stomach enzyme and will be accumulated.

The Lysosomal dysfunction will be result of accumulation of undigested polymer including inflammation which play important roles in pathophysiology, that reflect reduction in lysine acylation followed by reduction in aminoacyl tRNAs which promote Phe and E coli functions for activating protein and mRNAs synthesis, that will be followed by increasing in TNf-a synthesis (and reduction in VEGF-As) whichh activate NK (not beings related to human immune proper function) which regulated by the undigested polymers in random pathways stimulated by TNf-a functional pathway (activated by NLRP3 inflammasome.

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

Lysine acetylation so important to regulates the activity of Escherichia coli S-adenosylmethionine synthase . RNA (produced by E coli) is 2'-O-methylated demonstrated higher stability that can improve immune by promoting anti-inflammatory processes and improve myocardial functions, and adopt heart constriction by activating NR4As pathway.

The antihypertensive pathway mechanism is: the Lysine \rightarrow activate ATPase(stimulate retinoic acid "RA") \rightarrow Lysine acetylation \rightarrow promote Phe/ hydroxylase \rightarrow followed by \rightarrow activate Tyr/ hydroxylase \rightarrow activate dopamine \rightarrow activate NR4As pathway \rightarrow GC-beta \rightarrow activate both of Oxytocin and Nrf2 \rightarrow Ang2-AT2 and VEGF-A productive functions \rightarrow heme oxygenase \rightarrow anti-inflammatory growth and processes .

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

The oxidation of phenylalanyl-tRNA synthetase

Positively regulates translational quality control, and regulates the initiation of digestive enzyme mRNA translation, where consecutive AAA-lysines is paused for encoding Phe followed by ribosome sliding on homopolymeric A sequence .

That lysine activate mitochondria function followed by promoting Phenylalanine and phenylalanine-tRNAs productions by translations within E coli, followed by Phe/ hydroxylase activate Tyr hydroxylase production which activate dopamine synthesis.

And positively, Lysine is the most effective amino acid for activating all of ATPase, GTPase, and lysosomes, and E coli functions, where ATPase necessary for activating lysine Phosphoryl-

ation for activating lysosome digestion, followed by activating E coli through activating Phe hydroxylase production, while GT-Pase necessary for activating mitochondrial repairs, which act on pro-inflammation and cholesterol for activating estrogen production and activating the NR4As pathway which activate all of Oxytocin, Nrf2 followed by Ang2-AT2 and VEGF-A production and then followed by activating heme oxygenase and anti-inflammatory growth and processes that prevent LV-hypertrophy, and prevent coronary calcification

4. 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 TNF α which activate the increasing in NLRP3 inflammasome functions.

Lysosomal dysfunction is associated with increasing in TNF α and decreasing in VEGF-A:

Lysosome disruption caused by myocardial cell necrosis was responsible for the initial rise in plasma lysosomal enzyme activity and that the subsequent inflammatory reaction gave rise to the second peak. Topic: myocardial infarction, acute cardiac myocytes [1].

And, Danon disease caused by impaired autophagosome/lysosome fusion and which displays very severe cardiomyopathy phenotypes. [2].

And, tumor necrosis factor-alpha can reduce vascular endothelial growth factor receptors. [3].

And the Increasing in TNF α is related to decreasing in lysosomes and decreasing in myocardial function. Where, TNF-alpha down-regulates expression of both VEGF receptors in human endothelial cells [4]

The Lysosomal dysfunction is associated with decreasing in VEGF-A and increasing in TNF α , where TNF α activate NLRP3 inflammasome pathway functions followed by enhancement the cardiovascular pathologies development.

That the Lysosomal dysfunction is associated with NLRP3 inflammasome activation. [5].

And the TNF-a regulates transcription of NLRP3 inflammasome components and inflammatory molecules. [6]

Also, TNF- α enhanced the development of a number of cardiovascular diseases. [7]

Also, Patients with acute myocardial infarction had statistically significant increased serum levels of PTEN & TNF- α gene activity. [8]

That, Pretreatment with L-arginine and L-lysine reverses the

elevated levels of LDL- cholesterol probably by regulating cholesterologenesis and/or due to its inhibitory effect on lipid peroxidation, thereby reducing the level of lipid components against ISO-induced myocardial infarction. [9]

And results confirm the combined efficacy of L-arginine and L-lysine in alleviating isoproterenol induced mitochondrial damage. [10]

So, L argenine and Lysine have important roles in alleviating mitochondrial damage and so has its important role in reducing cholesterol aggregates.

Also, the Tumor Necrosis Factor- α (TNF α) promotes and exacerbates calcification in heart valve myofibroblast populations. [12]

So réduction in lysine can promote the increasing in TNF α followed by increasing in calcification.

Where, the TNF- α antagonism is unlikely to be a beneficial therapeutic strategy in patients with acute myocardial infarction. [13]

Also, the TNF- α blockade may improve insulin resistance and lipid profiles in patients with chronic inflammatory diseases. [14]

And, Genetically-predicted TNF levels were positively associated with coronary artery disease (odds ratio (OR) 2.25; 95% confidence interval (CI) 1.50, 3.37) and ischaemic stroke (OR 2.27; 95% CI 1.50, 3.43), and inversely associated with overall cancer (OR 0.54; 95% CI 0.42, 0.69. [15]

While, Lysine Prevents Arterial Calcification in adenine-induced uremic rats. [16]

And, the Myocardial Upregulation of Cathepsin D by Ischemic Heart Disease Promotes Autophagic Flux and Protects Against Cardiac Remodeling and Heart Failure. [17]

Where, Lysine is the common determinant for mannose phosphorylation of lysosomal proteins. [18]

So, L-lysine which important to activate lysosomal Functions Protects Against Cardiac Remodeling and Heart Failure, and important to Prevents Arterial Calcification (through activating lysosome digestive functions and enhancing OPA1 function mediated by aminoacyl tRNAs production which regulate Phe and E coli functions). [19]

Also, VEGF family is great potential for treating Coronary Heart Disease "CHD". [20]

So reduction in lysine promote TNF α and reduce VEGF-A production which will be followed by coronary artery disease, followed by reduction in neuroprotective effects on hypoxic motor neuro, and decreasing in the protection against memory impairment.

Where, VEGF-A also has a neuroprotective effect on hypoxic motor neurons, and is a modifier of ALS (amyotrophic lateral sclerosis). [21]

Also it is important to note that: VEGF A in serum protects against memory impairment in APP/PS1 transgenic mice by blocking neurophil infiltration. [22]

While, TNF- α promotes inflammation by increasing blood neutrophil concentrations. [23]

So it's clear that as VEGF-A inhibited as TNF α increased followed by the increasing in calcification in heart valve myofibroblast populations.

And, the Lysosomal dysfunction is associated with decreasing in VEGF-A and increasing in TNF α , where TNF α activate NLRP3 inflammasome pathway functions followed by enhancement the cardiovascular diseases, myocardial infarction.

Where, Lysine and Arginine protect from Mitochondrial Dysfunction followed by protection from Arterial calcification, mediated by activating lysosomal function which protect Against Cardiac Remodeling and Heart Failure.

VEGF family is great potential for treating Coronary Heart Disease "CHD

Where lysine has effective role in activating Phe hydroxylase and E coli and mitochondrial OPA1 functions followed by GC-beta and B-arrestine production followed by VEGF-A synthesis which treat Coronary Heart Disease "CHD and activate both of heme oxygenase and anti-inflammatory growth followed by modifying the ALS (amyotrophic lateral sclerosis, mediated by B-adrenergic and Nrf2 production.

Where defect in Lysine will cause lysosomal dysfunction and mitochondrial damage followed by decreasing in VEGF-A and increasing in TNF α which cause CVD and vascular calcification.

The lysosomal dysfunction will cause accumulation of undigested polymer including inflammation and cholesterol which play important roles in calcification.

5. Lysine is the Main Regulator for E Coli Proteins Where Both Lysine And Phenylalanine Important for Treating Pulmonary Disease

Firstly, pulmonary diseases characterized by increasing in cholesterol, and so Associated with defect in estrogen biosynthesis (where cholesterol is the substrate of estrogen synthesis regulated by synthase), that it has been approved that

Estrogen Inhibition Reverses Pulmonary Arterial Hypertension and Associated Metabolic Defects. [24]

Estrogen deficiency reflect deficiency in OPA1 repair and decreasing in both synthetase and synthase functions (where synthetase is main regulators for amino acids synthesis, while synthase is main regulator for beta subunits synthesis), that reflect deficiency in synthase function which responsible to regulate beta subunits by acting on cholesterol for producing estrogen .

So we can can conclude that estrogen Inhibition Reverses Inhibition in mitochondrial function and Inhibition in VEGF-A synthesis followed by increasing in TNF α , and then followed by Pulmonary Arterial Hypertension then calcification .

Estrogen is one of the steroid hormones synthesized from cholesterol. And Cholesterol is transferred from the cytoplasm to the mitochondrion by steroidogenic acute regulatory protein (StAR). [25]

lesterol. And Cholesterol is transferred from the cytoplasm to the mitochondrion by steroidogenic acute regulatory protein (StAR). [25]

As we mentioned lysosome is the main key for activating E coli which is the main for leucine-responsive regulatory protein STAR production which necessary to Modulates Mitochondrial Biogenesis and SIRT1-AMPK.

That studies approved that: Lrp (leucine-responsive regulatory protein) is a major Escherichia coli regulatory protein which regulates expression of a number of opérons. [26]

Where, GAA Glu \leftrightarrow CTT Leu

Lys AAG is the reversed copy of Glu GAA where both are having imp role in activating leu CTT which important for activating mitochondria.

And lysine AAA, & AAG has important role in activating GTPase production which important for modulating mitochondrial Biogenesis.

That, studies have shown that the activation state of RAS can be controlled by lysine ubiquitylation and acetylation . [27]

And 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, leading to contact untethering . [28]

And, also Ras proteins control mitochondrial biogenesis and function. [29]

So, lysine has important role for activating Glu, and leucine and activate GTPase production which necessary for mitochondrial Biogenesis mediated by lysine acetylation production which necessary for activating heart functions .

That, Lysine Acetylation Activates Mitochondrial Aconitase in the Heart mediated by activating E coli and production of mRNAs, where mRNAs produced by E coli activate NR4As pathway and followed by the stability of activating anti-inflammatory processes mediated by lysine acetylation and lysine hydroxylase productions followed by phenylalanine hydroxylase synthesis followed by tyrosine hydroxylase productions which necessary for dopamine synthesis.

It has been approved that: Lysine Acetylation Activates Mitochondrial Aconitase in the Heart. [30]

Also, the Lysine Methyltransferase SETD7 (SET7/9) Regulates ROS Signaling through mitochondria and NFE2L2/ARE pathway. [31]

So again lysine Acetylation Activates Mitochondrial Aconitase in the Heart through activating GTP-bound Rab7 which promotes mitochondria-lysosome contact site. And now it is clear that lysine function is necessary for promoting estrogen synthesis too that prevent cholesterol accumulation and then prevent aorta cal-

cification.

Also, the lysosome are highly necessary for activating E coli functions through lysine acylation which necessary for activating phenylalanine hydroxylase which promote E coli functions for producing stable active mRNAs.

That Lysine Acetylation Enhances Protein Aggregation and E. coli Viability. [32]

And , Lysine is necessary for Phenylalanine synthesis through translation processes (lysine AAA, AAG \leftrightarrow Phe TTT, TTC) which is the most important process for activating E coli and both protein and genes synthesis by E coli.

That the Regulation of Translation is occurred by Lysine Acetylation in Escherichia coli. [33]

And, Regulation of several metabolic and antioxidant pathways was observed at the level of protein expression and lysine acetylation, revealing a coordinated response involving transcriptional and post-translational regulation. [34]

So, lysine acylation has own important role in promoting antioxidant functions through activating mitochondrial function mediated by GTPase production.

And, lysine fatty acylation of an anchoring protein mediates adipocyte adrenergic functions (which has the antioxidant function). [35]

Also, The Phe hydroxylase promote antioxidant functions, through it's role in Contributing the Endophytic Bacterium *Pseudomonas fluorescens*' Melatonin Biosynthesis. [36]

So, Lysine acetylation activate both lysosomes and E coli functions necessary to activate proper cellular metabolism and proper antioxidant mediated by Phe /hydroxylase production which considered as stable mRNAs produced by E coli for modulation heart function and modulate antioxidant through activating dopamine and NR4As pathway which necessary for improving heart functions.

That, RNA (produced by E coli) is 2'-O-methylated demonstrated as higher stability (regulated by ATR & by both lysine H & Phe hydroxylase) for improving immune and activating the high stability of anti-inflammatory processes, and improving heart function. [37]

So, again Lysine Acetylation is so necessary for DNA and RNA methylation (mediated by activating GTPase production which necessary for mitochondrial Biogenesis) and is important for heart development, [38] mediated by Activating Mitochondrial Aconitase in the Heart and activating E coli functions (with availability of Phe which necessary for E coli for protein and for dopamine production), followed by production of mRNAs which necessary for DNA methylation and important for activate NR4As pathway and followed by the stability of activating anti-inflammatory processes.

So in brief, The decreasing in lysine acetylation production that will reflect decreasing in GTPase, followed by decreasing in OPA1 synthase (decreasing in mitochondrial repairs), and followed by decreasing in translation process which necessary for Phenylalanine and Phe hydroxylase production, then followed by increasing in cholesterol accumulation, and decreasing in heart function, and increasing in calcification in blood vessels .

Notice, arginine is necessary to be included in mRNAs which produced by by E coli and necessary to be included in both lysine acetylation and phenylalanine hydroxylase to perform its function to prevent aortic calcification (mediated by tRNAs production regulated by Arg).

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. [39]

And, Homo-arginine Supplementation Prevents Left Ventricular Dilatation and Preserves Systolic Function in a Model of Coronary Artery Disease. [40]

Some studies reported that acetylation can promote calcification!! Increases in Ach3 and Ach4 due to inhibition of HDACs promote vascular calcification [41]

If Acetylation will not produced properly in vivo in a proper balance with phe/hydroxylase synthesis, means is reflecting lysosome dysfunction and E coli dysfunction too, that TNF α will be increased, and calcification will be improved in vivo causing CVD , that decreasing in Lys acetylation will reflect decreasing in phenylalanine/ hydroxylase productions with decreasing in both E coli functions and dopamine synthesis .

Where, Phenylalanine necessary to promote mitochondrial function (mediated by RhoA/Rho-associated kinase pathway which activated by lysine) which necessary for promoting estrogen synthesis from cholesterol which is the substrate for pervious synthesis , that , it has been reported that it has been reported that : Phenylalanine activates the mitochondria-mediated apoptosis through the RhoA/Rho-associated kinase pathway in cortical neurons. [42]

And dopamine (which inhibited due to Inhibition in phenylalanine and in Phe /hydroxylase synthesis) affects ventilation, pulmonary circulation, bronchial diameter, neuromodulation of sensory pulmonary nerves and lung water clearance. Through these complex mechanisms, DA may exert beneficial as well as detrimental effects on respiration. [43]

And, other studies indicated that: dopamine-related genes may play a role in the progression of COPD. [44]

Also, the decreasing in pyrimidine kinases (pyrimidine synthesis regulated by OPA1 synthetase) reflect decreasing in phenylalanine hydroxylase and decreasing in mitochondrial function, that may mediated by reduction in Lys acetylation followed by reduction in GTPase production and reduction in mitochondrial function , that

can be the result of reduction in estrogen synthesis and decreasing in dopamine synthesis, which followed by aorta calcification and pulmonary disease.

Where, studies reported that: Deficiency in pyrimidine kinases cause cholesterol accumulation and increase the risk of coronary artery Disease. [45]

But in case of phenylketonuria characterised by decreasing in Phe hydroxylase followed by decreasing in dopamine and increasing in the undigested polymers which due to decreasing in lysosomal function, that 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. [46]

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. [47]

Also, phenylalanine through activating the mitochondrial function protect 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. [48]

And, inhibitory effects of PCPA on MCT-induced inflammation and arterial remodeling are related to the downregulation of the NFAT-1 and NF- κ B signaling pathways. [49]

Lysosomal dysfunction cause decreasing in both lysine Methylation and phenylalanine hydroxylase followed by defect in mitochondria that cause calcification:

As we mentioned before lysine phosphorylation is the main activator for lysosomal function, where studies indicated that: the Loss of laa-1 transporter caused accumulation of lysine and arginine in enlarged, degradation-defective lysosomes. [50]

And, lysine residues are required for phosphorylation of procathepsin L and are a common feature of the site on many lysosomal proteins. [51]

And, Lysine phosphorylation necessary for regulating E coli functions, that both lysine supplementation and lysine biosynthesis enhancement improved the high-temperature stress tolerance of E. coli cells. [52]

So it's clear the importance of lysine to activate lysosomal function and to improve E coli functions.

Also, Lysine biosynthesis enhance the phenylalanine translation functions (Phe TTT, TTC \leftrightarrow Lys AAA, AAG) where phenylalanine is important for building promoter within active genes and subunits mediated by lysine acetylation followed by both aminoacyl tRNA and Phe hydroxylase productions through activating E coli functions. That studies shows a significantly larger coefficient of repression than the other genes in the lysine synthesis pathway, which indicates the weak binding activity of the repressor to the

dapD promoter region. Moreover, there is a trend that the closer an enzyme is to the start of the lysine biosynthesis pathway, the smaller its maximal promoter activity is. [53]

So lysine biosynthesis absolutely connected to Phenylalanine productive functional pathway, where both are promoting mitochondrial functions but Lysine is First activator key for mitochondrial functions that Lys responsible for producing GTPase which necessary for mitochondrial repairs followed by phenylalanine functional activities which necessary for providing TTT TTC and fir building active promoters within genes and subunits.

The necessity of the Regulation of lysine methylation emerged as a critical regulator of neurological function and disease. [54]

The decreasing in lysine cause decreasing in lysosomal function that will be the result of accumulated undigested polymers which cause lysosomal enlargement, followed by decreasing in lysine acylation and decreasing in aminoacyl tRNAs, that followed by decreasing in Phe hydroxylase which cause decreasing in Tyr hydroxylase followed by decreasing in E coli and in dopamine production.

Inhibition in lysine will reflect Inhibition in methylation (which can cause mutation in DNA) and reduction in mitochondrial functional passway, followed by reduction in both of pyrimidine kinases, and estrogen (which required for pulmonary alveolar formation), that will cause cholesterol accumulation which can be aggregated with undigested polymers in blood vessels.

That it has been approved that, estrogen receptors, are required for the formation of a full complement of alveoli in female mice. [55]

Now, we can understand why lysine is so important for treating pulmonary disease, which done through its phosphorylation roles in activating mitochondrial functions and both of lysosomes and E coli functions mediated by Lys acylation and Phe hydroxylase production, which produced by translation processes of lysine for producing Phenylalanine stability (Phe TTT TTC \leftrightarrow Lys AAA, AAG) mediated by GTPase production (which activate mitochondrial repair and functions).

Where, 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. [56]

As lysine decreased as phenylalanine / hydroxylase decreased, followed by decreasing in Tyr hydroxylase and in E coli functions followed by reduction in dopamine biosynthesis.

That Inhibition in dopamine (due to Inhibition in both of Lys /hydroxylase and Phe hydroxylase) is Associated to phenylketonuria and connected to lysosomal dysfunction.

That, Phenylketonuria (PKU) is an autosomal recessive disorder caused by reduction in phenylalanine hydroxylase, which required to tyrosine hydroxylase synthesis, which is essential for dopamine

production. [57]

And, adult Patients Suffering from Phenylketonuria are suffering from reduction in Cerebral Fluoro-l-Dopamine Uptake. [58]

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, that will cause accumulation in phenylalanine (due to reduction in all of Lys/acetylation, lysine hydroxylase and Phe/hydroxylase) followed by reduction in Tyr hydroxylase and reduction in all of GTPase and reduction in mitochondrial function, that will cause reduction in dopamine synthesis. [59]

So, the lysosomal damage is connected to phenylketonuria and Associated with reduction in dopamine that reflect reduction in lysine acylation and reduction in Phe hydroxylase followed by reduction in Tyr hydroxylase which associated with increasing the risk of phenylketonuria and decreasing in dopamine production.

The lysine play so important role in activating both of lysosome and E coli including promoting protein synthesis mediated by GTPase production which activate mitochondrial function, followed by activating NR4A pathway which increase the enhancement of antioxidant productive functions started by glucocorticoid-beta production followed by oxitocin and Nrf2 production, that Lys has important roles in increasing the affinity of protein synthesis and evaluating the biological cellular regulation through sharing its functions with phenylalanine function for activating E coli functions and Phe hydroxylase productive functions.

Also, lysine fatty acylation increases proteins affinity by E coli functions (mediated by phenylalanine hydroxylase synthesis) which necessary for cellular membranes Vibrant. functionality. [60]

Also it has been approved that: Lysine acylation in Escherichia coli regulates enzyme activity and lactate synthesis. [61]

The lysine acylation necessary for activating E coli, and allows the actual effects of lysine acylation for protein productive functions. [62]

The lysine acylation is important for Mitochondrial acylation which regulates protein productive functions in human diseases mediated by activating E coli which mediated by phenylalanine hydroxylase production. Where, protein lysine acylation is a key PTM coordinating mitochondrial processes. [63]

6. The Lysosome dysfunction associated with decreasing in lysine with increasing in inflammations and in inflammasome NLRP3 function followed by increasing in the risk of cardiovascular disease

The increasing in inflammations and increasing in accumulated Phe is due to the absence of Lysine (which necessary for activating lysosome digestive functions and Lysine hydroxylase), that asso-

ciated with deficiency in Lysine/ acylation followed by decreasing in both of lysine hydroxylase and Phe hydroxylase which followed by decreasing in E coli functions, Followed by decreasing in aminoacyl-tRNAs production, and in protein biosynthesis mediated by decreasing in mRNAs efficiency (which produced by E coli), and followed by cholesterol precipitation, and undigested polymers precipitation in blood vessels and increasing in their level in plasma, that will be the result of increasing in pulmonary disease and cardiovascular disease.

Also, the lysosomes dysfunction is due to lysine dysfunction which associated with Phe instability with decreasing in aminoacyl tRNAs followed by E-coli dysfunction and insufficient protein biosynthesis affinity, that will lead to abnormal autophagy and reduction in NR4A pathway and reduction in antioxidant affinity.

That, studies approved that Defective lysosomes lead to abnormal autophagy, activation of inflammation, and reduction in the infection control. [64]

And the Lysosomal damage has been implicated in NLRP3 inflammasome activation (NLRP3 is an important Innate immune sensor that responses to various signals and forms the inflammasome complex, leading to IL-1 β secretion and pyroptosis) in response to crystals or particulates. [65]

And, The Lysosomal dysfunction is associated with NLRP3 inflammasome activation in chronic unpredictable mild stress-induced depressive mice. [66]

So Lysosomal damage reflect lysine dysfunction and increasing in undigested polymers and inflammation followed by defect in E coli and decreasing in the normal autophagy production, which implicated with increasing in NLRP3 inflammasome complex (which regulated by TNF α), that can be associated with decreasing in the affinity of protein synthesis.

The lysosome dysfunction is associated with decreasing in both lysine acylation and Phe hydroxylase (which lead to phenylalanine accumulation) and increasing in inflammations that increase the TNF- α production which activate NLRP3 inflammasome activities that will increase the risk of CVD and decrease the dopamine synthesis (which regulated by Phe hydroxylase and tyrosine).

That, The Activation of Inflammation in Patients with Cardiovascular Disease Are Associated with Higher Phenylalanine to Tyrosine Ratios. [67]

So, Patients with Cardiovascular Disease are having decreasing in all of lysosome, mitochondria, and E coli functions that followed by reduction in lysine methylation followed by reduction in Phe hydroxylase that those patients are having accumulation in phenylalanine that they can have the risk of Phenylketonuria.

Also, dysregulation of lysosomal pathways in the cardiovascular system contribute to disease in a highly context-dependent man-

ner. [68]

That, dysregulation of lysosomal pathways in the cardiovascular system reflect sever decreasing in lysine and in lysine acylation followed by reduction in phenylalanine / hydroxylase (that will lead to phenylalanine accumulation) that will lead to higher Phe-nylalanine to Tyrosine Ratios, followed by reduction in the normal E coli functions followed by increasing in inflammation which activate TNF-a production, which activate NLRP3 inflammasome activities.

Where, Lysine functions Prevents Arterial Calcification. [69]

And, studies approved that: L-Lysine treatment significantly reduced the magnitude of lipid peroxidation, wet/dry ratio of lung tissue, tumor necrosis factor alpha, interleukin-8, and macrophage inhibitory factor levels. [70]

Increasing in lysosomal dysfunction cause increasing in inflammation followed by increasing in TNFa and increasing in un-digestive polymers, that will cause increasing in Phe ratio.

That the increasing in digestive polymers (which include inflammations) reflect increasing in TNFa production.

And, the Microglial activation and TNF α production mediate altered CNS excitability following peripheral inflammation. [71]

So lysosomal dysfunction (regulated by lysine phosphorylation) is associated with decreasing in Lys acetylation and decreasing in Phe hydroxylase followed by accumulation in Phe “TTT, TTC” (due to decreasing in Lys “AAA, AAG” which necessary for Phe stability’s functions), and followed by decreasing in mitochondrial functions then followed by increasing in inflammations, and increasing in the risk of calcification, cardiovascular disease, and pulmonary diseases.

That, L-lysine is important to decreases nitric oxide production and increases vascular resistance. [72]

And The hypertension in pulmonary disease due to lysosomal dysfunction and decreasing in OPA1 function, that cause increasing in cholesterol (with decreasing in estrogen synthesis) and accumulation of undigested polymers including inflammation with reduction in amino acyl tRNAs which regulate the proper affinity protein synthesis, that will lead to variation in protein synthesis by E coli that will cause abnormal autophagy , followed by increasing in inflammasomes complex, that cause reduction in infections control.

The L-Lysine is so important to Prevents Arterial Calcification (through activating lysosome and enhancing OPA1 function mediated by aminoacyl tRNAs production which regulate Phe and E coli functions). [73]

And, L-lysine supplementation improve glycemic control, decrease protein glycation, and insulin resistance. [74]

The lysine acylation is necessary for aminoacyl tRNA produc-

tions which activated by Phe /hydroxylase and E coli followed by activating mitochondrial function which necessary to activate glucocorticoid beta followed by β -arrestin production and both of oxytocin 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.

Also, the suppressing of pro-inflammation reflect the activation of proper function of both lysosome and E coli followed by reprogramming the normal macrophage production followed by activating anti-inflammatory processes.

That, the lysosome not only is a place for cargo degradation but also plays crucial roles in regulating macrophage polarization. [75]

Where, Nrf2-mediated anti-inflammatory polarization of macrophages. [76]

And, the activation of Nrf2 will reprogram macrophage intermediary metabolism and suppresses the type I Interferon (suppress pro-inflammation). [77]

So, lysosomal function is responsible for activating Nrf2 production through activating NR4A pathway, mediated by activating E coli proper functions, that will suppresses the type I Interferonand.

Also, Oxytocin alleviates liver fibrosis via hepatic macrophages. [78]

And, inflammation upregulated OXTR transcription (as we mentioned previously) 10- to 250-fold relative to control in THP-1 and human primary macrophages and increased OXTR protein expression (mediated by promoting lysosomes and E coli functions). [79]

So, oxytocin regulated by lysosome functions and mediated the polarization of macrophages (regulated by lysosomes function), that promote myocardial function via macrophages production mediated by activating NR4As pathway which promote GC-beta, B-arrestine, B adrenergic production followed by oxytocin “OT” and Nrf2 production.

Also, the Treatment with oxytocin reduces the expression of proinflammatory cytokines and reduces immune cell infiltration. And also Oxytocin stimulates differentiation stem cells to cardiomyocyte lineages as well as generation of endothelial and smooth muscle cells, promoting angiogenesis. [80]

And, the OT treatment of mesenchymal stem cells stimulates paracrine factors beneficial for cardioprotection.[81]

7. Role of Phenylalanine and Lysine in Dopamine Synthesis and in Cardiac Functions

Firstly, increasing in phenylalanine alone (with decreasing in phenylalanine hydroxylase followed by lysosomal dysfunction) predicts mortality in critical patients with heart failure, due to absence of phenylalanine hydroxylase (which due to absence of both lysine

and OPA1 functions which are main regulator for hydroxylase productions), that those patients suffer from a lack of aminoacyl tRNA productions and they suffer from lysosome and E coli dysfunctions. [82]

And The phenylalanine/phenylalanine hydroxylase modulation as a potential therapeutic strategy for age-associated cardiac impairment. [83]

That Phe hydroxylase is so important to enhance the dopamine synthesis and epinephrine production, that Firstly, activate tyrosine hydroxylase production followed by L-DOPA. DOPA synthesis which converted to dopamine to epinephrine production. [84]

Also, Lysine and cysteine is necessary for dopamine production.

That, DOPAL reactivity is due to both the aldehyde and the catechol moiety, respectively resulting in covalent modification of primary amines and thiols (i.e. lysine and cysteine residues of proteins). [85]

And in other studies approved that Lysine Acetylation Contributes to the Pathogenesis of Parkinson's Disease. [86]

Where, parkinson Diseases characterized by depletion of dopamine. [87]

Now, lysine is so necessary for dopamine productive functions through its acylation which enhance Phe hydroxylase which necessary for dopamine production, where the depletion of lysine, Phe hydroxylase and dopamine will be the rest of Parkinson's disease.

Also, Phe has been approved as is so important for immune activation and stimulation that is an a sensor to any change that affect on immunity, where as calcium activated as Phe functions is stimulated to activate E coli for adopt calcium ratio through activating related mRNAs production by E coli (mediated by aminoacyl-tRNAs regulated by lysine acylation). [88]

Phenylalanine is closely related to dopamine, epinephrine (adrenaline), and tyrosine.

And increasing in phenylalanine will stimulate mitochondrial Cox functions for reactivating mTORC1 production and reactivate aminoacyl tRNA production "through lysine acylation functions " which activating E coli for reproduce protein synthesis and related mRNAs for reactivating NR4As pathway and then adopt heart constriction and functions throughout producing oxytocin and Nrf2 followed by Ang2-AT2 and VEGF-A production for anti-inflammatory purposes. [89]

And, Phenylalanine is so Important for Regulating the Capacity of Intestinal Immunity, Antioxidants and Apoptosis (notice in availability of lysine acylation and in availability of Phe/ hydroxylase production). [90]

In the other side, in patients whose the Increasing in phenylalanine alone (whose are having decreasing in phenylalanine hydroxylase and with lysosomal dysfunction) predicts mortality in critical patients with heart failure,

The Nuclear ATR lysine-tyrosylation protects against.

Heart failure by activating DNA damage response (mediated by reactivating lysosomal Functions). [91]

That, lysine-tyrosylation mediated by lysine acylation which so imp for aminoacyl tRNA production which important for activating phenylalanine hydroxylase for dopamine synthesis and activating the E coli functions for protein synthesis.

That, Acetylation of lysine ϵ -amino groups regulates aminoacyl-tRNA synthetase activity in Escherichia coli. [92]

And, Lysine promote ATPase (>Pase which activate mitochondrial repair) which promote lysine-acetylation to regulates the activity of Escherichia coli S-adenosylmethionine synthase. [93]

Lysine Firstly activate lysosome functions through Firstly promoting ATPase function which increase phosphorylation on lysosomes surface followed by activating lysine-acetylation and Phe/hydroxylase which responsible for activating E coli and protein synthesis, and activate dopamine production mediated by Tyr hydroxylase production.

That Lysine-based structure responsible for selective mannose phosphorylation of cathepsin D and cathepsin L defines a common structural motif for lysosomal enzyme targeting. [94]

The lysine dysfunction followed by defect in ATPase production, followed by defect in lysosomes function , followed by defect in Phe hydroxylase, and defect in E coli, followed by accumulated phenylalanine, which can explain why phenylalanine is accumulated in the cases of phenylketonuria patients.

Finally, Nuclear ATR lysine-tyrosylation protects against

Heart failure by activating DNA damage response (mediated by activating Phe Hydroxylase synthesis, and activating E coli by lysine acetylation, followed by mRNAs production and dopamine production). [95]

And, the RNA (produced by E coli) is 2'-O-methylated, and demonstrated as higher stability (regulated by ATR & by both lysine hydroxylase & Phe hydroxylase) that can improve immune for high anti-inflammatory processes stability and so will improve heart impact functions.

That it has been approved that: the RNA fragments could be 2'-O-methylated and demonstrated higher stability but lower translation efficiency. [96].

8. Lysine regulate Dopamine synthesis (which considered as Antihypertensive Counterbalance) is important for controlling myocardial constriction

Firstly, Tyrosine Hydroxylase Regulate Dopamine Synthesis, and studies approved that : the Tyrosine 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. [97, 98]

Where, Phenylalanine hydroxylase converts phenylalanine to ty-

rosine, tyrosine hydroxylase hydroxylates tyrosine to L-DOPA. [99]

And, studies approved that:

Dopamine synthesis begins with the amino acid phenylalanine, and proceeds sequentially through tyrosine, DOPA, and then dopamine. [100]

And, it has been approved that: Phenylalanine (Phe) and tyrosine constitute the two initial steps in dopamine biosynthesis. [101]

Also, phenylalanine 3-hydroxylase (Phe3H) catalyzes the synthesis of meta-Tyr. [102]

And phenylalanine hydroxylation is so important in vivo to adopt the tyrosine ratio, where in the phenylalanine hydroxylation deficiency the tyrosine ratio will decreased followed by decreasing in dopamine and reflect reduction in NR4As pathway followed by reduction in both of heme oxygenase and anti-inflammatory processes.

Where, studies approved that: in vivo the phenylalanine hydroxylation regulate tyrosine. [103]

So, lysine play important roles in activating and improving the lysosomes and E coli functions (as discussed before) and play important roles in activating Phe hydroxylase and then the Tyr hydroxylase, and consequently regulate dopamine synthesis.

The lysine acetylation is so important for improving E coli functions, that by translation encodes Phe in E coli that improve protein and genes production.

That it has been approved that, Lysine Acetylation Is a Highly Abundant and Evolutionarily Conserved Modification in Escherichia Coli. [104]

Lysine codon has so important effect on translation and protein levels through encoding phenylalanine “TTT, TTC “ which adopt protein production where consecutive lysines is paused for encoding Phe “TTT, TTC “ within protein chains and genes, that Phe codon also is used for building active promoter within the active protein chains.

That, the Kinetic studies in E. coli reveal that differential protein production results from pausing on consecutive AAA-lysines followed by ribosome sliding on homopolymeric A sequence. Translation in a cell-free expression system demonstrates that diminished output from AAA-codon-containing reporters results from premature translation termination. [105]

And also studies approved that, positively the oxidation of phenylalanyl-tRNA synthetase regulates translational quality control. [106]

And, studies reported that Phenylalanine regulates the initiation of digestive enzyme mRNA translation. [107]

So, positively the oxidation of phenylalanyl-tRNA synthetase regulates translational quality control, and regulates the initiation of

digestive enzyme mRNA translation, where consecutive AAA-lysines is paused for encoding Phe followed by ribosome sliding on homopolymeric A sequence .

And Lysine activate aminoacyl tRNAs “Lysine tRNA synthetase or lysyl-tRNA synthetase” (regulated by retinoic acid) that lysine activate mitochondria function which promote Phenylalanine and phenylalanine-tRNAs productions within E coli.

And lysine phosphorylation activate E coli functions through activating L-phenylalanine production (by translation) which upon mitochondrial function will improve Phe-tRNA productions which activate Tyr hydroxylase which activate dopamine synthesis.

The Dopamine increase the force of contraction, and increase the elevation of the beating rate, and the constriction of the coronary arteries. [108]

And now we can understand the mechanism of dopamine how is promoting antihypertensive pathway!! Through lowers blood pressure. That studies shown that: Dopamine considered as important for promoting antihypertensive pathway, through lowers blood pressure. [109]

And, Dopamine Receptors: is considered as Important Antihypertensive Counterbalance Against Hypertensive Factors. [110]

Where, the antihypertensive pathway mechanism is : the Lysine methylation promote Phe/ hydroxylase \rightarrow followed by \rightarrow activate Tyr/ hydroxylase \rightarrow activate dopamine \rightarrow activate NR4As pathway \rightarrow GC-beta \rightarrow activate both of Oxytocin and Nrf2 \rightarrow Ang2-AT2 and VEGF-A productive functions \rightarrow heme oxygenase \rightarrow anti-inflammatory growth and processes.

The lysine activate lysosome followed by activating amino acyl-tRNAs (mediated by phenylalanine hydroxylase production) followed by activating mRNAs production by E coli, then followed by activating dopamine synthesis which mediated by Tyr hydroxylase synthesis (by Phe hydroxylase activity) which protect from hypertension.

Where, lysine acetylation and phosphorylation in E coli necessary for aminoacyl-tRNA synthetase synthesis (which activate previous antihypertensive pathway), that studies reported that: Acetylation of lysine ϵ -amino groups regulates aminoacyl-tRNA synthetase functions. [111]

Also it is reported that: L-lysine influences the selective brain activity in dependence on the biological significance of pain-induced behavior. [112]

So it is clear that The lysine is so important to improve cellular function through activating antioxidant (activating antihypertensive pathway) mediated by improving lysosomal Functions and both of Phe/hydroxylase and E coli functions followed by activating Tyr/ hydroxylase which necessary for activating dopamine synthesis , then followed by activating NR4As pathway which important for promoting oxytocin and Nrf2 production which neces-

sary for adopting antioxidant functions (mediated by GC-beta and B-arrestine synthesis).

And, it is reported that: the tyrosine hydroxylase "TH" is highly regulated notably by phosphorylation of several Ser/Thr residues in the N-terminal tail (which clearly regulated by Lys phosphorylation which necessary to activate lysosome, which then promote E coli functions as I mentioned before). [113]

And, the cetylation of lysine ϵ -amino groups regulates aminoacyl-tRNA synthetase activity in *Escherichia coli*. [114]

Followed by activating the Phe tRNAs production which necessary to promote Tyr hydroxylase production and dopamine synthesis.

So, together we can ensure that lysine acetylation are so important for activating the lysosomal function, and both of Phe hydroxylase and E coli functions for improving protein synthesis by E coli and dopamine synthesis which modulate heart functions and blood flow (mediated by Tyr/ hydroxylase synthesis which regulated by Phe/ hydroxylase).

Dopamine has important functions in cardiovascular system and endocrine pancreas, that Dopamine "DA" increases heart activity followed by increasing in blood pressure (depending on the Healthy condition of blood vessels, and on dopamine production level). [115]

Where, deficiency in Phe hydroxylase followed by decreasing in antihypertensive pathway and in Both of Tyr hydroxylase and dopamine synthesis will cause CVD. That it has been reported: cardiovascular phenotype is associated with Phe /hydroxylase deficiency in adult patients. [116]

Lysine Methylation has important role in adopting hypertension through activating pervious Antihypertensive pathway mediated by Phe hydroxylase synthesis and Tyr hydroxylase production followed by activating both of dopamine and NR4As pathway.

That, hypomethylation of the Toll-like receptor 4 (TLR4) gene in leukocytes mediates a part of the effect of particulate matter air pollution on blood pressure elevation. [117]

9. Retinoic Acid Adopt Myocardial Function by Modifying Mitochondria Mediated by Lys Acetylation and ROR-Beta Production which Activate Antidiabetic Functions

Retinoic acid is so necessary for Retinoic Acid Receptor-Related Orphan Receptors (ROR gamma, beta, and alpha "α" subunits) synthesis upon the mitochondrial regulation, that necessary for several functions during cellular metabolic functions, that reduces apoptosis and oxidative stress, evaluate cardiac development, enhances the repair of infarcted myocardium, and the all-trans retinoic acid "ATRA" is having important role in modulating cardiac mitochondria by promoting fission events, where retinoic acid has important roles in dissolving Aorta calcification too.

Retinoic acid have important roles in activating antidiabetic func-

tion, and antioxidant function, through activating NR4As pathway which activate oxitocin and Nrf2 production that explain how all-trans retinoic acid (ATRA) activate cardioprotective oxytocin-natriuretic (OT-NP) system, preventing apoptosis and collagen accumulation in hearts.

All-trans RA (ATRA) treatment improve the cardioprotective oxytocin-natriuretic peptides (OT-NP) system, preventing apoptosis and collagen accumulation.

The Retinoic acid (RA) established several functions during cardiac development, including actions in the fetal epicardium required for myocardial growth, (also, retinoic acid reduce oxidative stress). [118]

And Retinoic acid reduces apoptosis and oxidative stress by preservation of SOD protein level. [119]

Retinoic acid directly enhance cardiomyocytes activities and protects mouse hearts, and enhances repair of infarcted myocardium. [120, 121]

Also, the proteomic analyses of human and guinea pig heart failure (HF) were consistent with a decline in resident cardiac all-trans retinoic acid"ATRA". [122]

Also, All-Trans Retinoic Acid "ATRA" is having important role in modulating cardiac mitochondria by promoting fission events, and modify the ultrastructure of mitochondria in heart. [123]

The Retinoic acid increase the mRNA levels and protein synthesis of matrix Gla protein, and calcification inhibitory molecule, in human coronary artery and aortic valve cells. [124]

And, Retinoids enhance dissolving the calcification paradox. [125]

And retonic acid necessary to enhance the blockage and discard the binding toxicity of potassium through activating RORs pathway, that it's reported: Retinoic acid blocks potassium channels in human lymphocytes. [126]

Also, Retinoic acid modulates microglia through activating RORs pathway (ROR-gamma, ROR-beta, and ROR-alpha production), which induce the contractile phenotype of smooth muscle cells, also it controls endothelial-pericyte interactions. [127]

The reduction in ROR pathway reflect Diabetic cardiomyopathy. [128]

Where, retinoic acid activate the Estrogen expression mediated by ROR-beta production regulated by synthase function.

Where, it has been approved that: Estrogen regulates (promoted by and enhanced by retinoic acid and synthase function) the expression of retinoic acid synthesis enzymes and binding proteins. [129]

And it's so important to note that:

Both of retinoic acid and estrogens activate increasing in oxytocin gene expression (that RA has the antioxidant properties). [130]

So, retinoic acid upon lysine/hydroxylase functions activate both Phe / hydroxylase and E coli that activate the Estrogen expression

mediated by ROR-beta production regulated by synthase function followed by activating dopamine and all of B-adrenergic, oxytocin gene, and Nrf2 expression via activating NR4As productive pathway which it's important pathway for activating and adopting heart functions, where the activation of previous NR4As pathway by retinoic acid explain why RA has the role of antioxidant functions .

That, other studies indicated that: Vitamin A possesses antioxidant properties by directly scavenging reactive oxygen species, boosting antioxidant enzyme activity, antioxidant defence mechanisms. [131]

So, Vitamin A or retinol is the most multifunctional vitamin in the human enhance the ROR-beta and estrogen synthesis by synthase function followed by activating NR4As pathway which activate oxytocin and Nrf2 productive functions which are important for activating both of heme oxygenase and anti-inflammatory processes mediated by Ang2-AT2 and VEGF-A productive functions.

Also, it has been reported that: the all-trans RA (ATRA) treatment improve the cardioprotective oxytocin-natriuretic peptides (OT-NP) system, preventing apoptosis and collagen accumulation in hearts. [132]

Also, retinoids have important roles in activating antidiabetic function and antioxidant function, through activating NR4As pathway which explained by activating cardioprotective oxytocin-natriuretic peptides (OT-NP) system, preventing apoptosis and collagen accumulation in heart.

That it has been approved that: All-trans retinoic acid stimulates gene expression of the cardioprotective natriuretic peptide system and prevents fibrosis and apoptosis. [133]

And, 9-cis-retinoic acid stimulate estradiol and testosterone synthesis and might be caused by activation of P45017 α transcription via retinoid X receptor signaling. [134]

And, Retinoic acids (RAs) evoke an anticoagulant effect by up-regulating thrombomodulin TM and downregulating expression of tissue factor (TF) in acute promyelocytic leukemia. [135]

Also, vitamin A, plays a key role in the differentiation of T cell subsets, the migration of T cells into tissues, and the proper development of T cell-dependent antibody. [136]

The retinoids is regulators of vasculogenesis and smooth muscles cells "SMC" differentiation. [137]

10. The Lysosomal Dysfunction 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. Defects in lysine and in genes encoding lysosomal proteins cause lysosomal storage disorders, survival of tumor cancer, autoimmune disorders, blood disorders, Athero-

sclerosis, neurodegenerative diseases.

The lysosomal dysfunction promise accumulated phenylalanine, inflammation, and cholesterol deposit in arteries walls and exert calcification because of the accumulation of undigested polymers which included cholesterol and pro-inflammation.

The lysosomal dysfunction caused accumulation of the undigested inflammation, polymers, and accumulation of cellular waste, that also reflect the cholesterol accumulation.

As reported It's true that estrogen deficiency reflect diabetic disease and Estrogen Deficiency, Exacerbates Type 1 Diabetes-Induced Bone TNF- α Expression and Osteoporosis. [138].

The accumu"ated cholesterol is associated with undigested polymers due to lysosomal deficiency lead to cholesterol deposit in blood vessels

That Hyperlipidemia Promotes Osteoclastic. [139]

And, the Deposition of free cholesterol in the blood vessels in patients with coronary artery disease and atherogenesis. [140]

So Deposition of cholesterol in the blood vessels not only due to deficiency in estrogen biostatistics but also due to lysosomal dysfunction.

That, The lysosomal dysfunction has important role in atherogenesis. [141]

Also, coronary calcification not only due to estrogen deficiency but also due to lysosomal dysfunction, that reflect decreasing in lysine function and decreasing in Lys /hydroxylase followed by decreasing in Phe/ hydroxylase followed by reduction in Tyr hydroxylase and reduction in both of E coli functions and dopamine production, and reflect decreasing in both mRNAs (produced by E coli)

And in NR4As productive pathway which activate antioxidants functions.

That it has been approved that coronary calcification associated with osteoporosis. [142]

The Lysosomal dysfunction has important role in tumor survival in the same tissue.

As the lysosomes functional processes increased as the accumulated cholesterol, and polymers increased in their own main tissue.

Notice that both RA and lysine are having strong roles in activating lysosomes for activating anticoagulant and antioxidants functions which are so imp for preventing neurodegenerative Diseases, Aorta calcification, and tumor survival.

The disruption of Lysosome Function will cause decreasing or mutation to its functional pathway that will promote accumulation of undigested polymers and cholesterol that will be result of promoting NF- κ B production and pathogenesis including phenylketonuria, neurodegenerative diseases, aorta calcification, and tumor survival.

Where, it has been reported that : the disruption of Lysosome Function Promotes Tumor Growth. [143]

And, the Lysosome dysfunction cause neurodegenerative diseases. [144]

Lysosomes dysfunction contributes the cardiovascular disorders is known as lysosomal storage disorders. [145]

So, lysosome dysfunction contributes to cardiovascular disorders, neurodegenerative diseases, coronary calcification, and atherosclerosis.

11. Lysine Promote Anticoagulant, Antioxidant and Activate NAADP Followed by Anti-Calcifications

As described previously, Retinoic acid receptor- α regulates synthetic events in human platelets while lysine promise strong cooperation with RA to enhance anticoagulant function, and to Prevent calcification. [146]

Lysine-containing peptides can be used as promising antiplatelet drugs in prothrombotic conditions of the organism. [147]

Also, L-lysine attenuates pancreatic tissue injury by inhibiting the inflammatory cytokine IL-6 and enhance antioxidant pathway functions.

[148]

Both of lysine and RA are having the importance of activating antioxidant and anticoagulation processes.

While arginine promote tRNA synthesis which activate molecular migration that cooperate with lysine functional pathway to prevent coagulated molecules, that Mutations in tRNAs (regulated by Arg) is contributed to complex human diseases. [149]

And the defect in lysosomal Ca²⁺ messenger of nicotinic acid adenine dinucleotide phosphate (NAADP) reflect lysosomal dysfunction and accumulation in macrophages that contribute to coronary atherosclerosis .[150]

The adenine active binding in NAADP is formed by lysine “AAA, AAG” that Adenine can be distinguished from guanine based on the size and shape of the binding pocket and steric exclusion of the guanine N2 exocyclic amino group. [151]

The adenine nucleotides of lysine triplets “AAA, AAG “ is considered as the Main key to promote ATPase and can promote useful Adenosine derivatives “ADR” in vivo, followed by activating phosphorylation on lysosomed and activating E coli by promoting Phe/ hydroxylase followed by dopamine synthesis, then followed by activating antioxidant productive functions via activating NR4As pathway as discussed previously .

That it's reported that Adenosine Derivates is Antioxidant Agents: Synthesis, Characterization, and the antioxidant functions of Adenosine derivative (ADR) was dependent on the concentration of the ADR. [152]

And, the deficiency in lysine reflect deficiency in lysosome function followed by deficiency in both of Phe/ hydroxylase and E coli, followed by defect in antioxidant functions which followed by coronary calcification , that Lysosomal dysfunction exacerbates vascular calcification. [153]

The Lysine “AAA, AAG” function activate lysosomes through providing the adenine nucleotides which necessary for ATPase synthesis , and NAADP production that enhance lysosome phosphorylation functions and its digestion functions, that enhance cardiac function through promoting mitochondrial fusion and function followed by activating E coli functions, followed by activating antioxidant functional pathway mediated by decreasing pro-inflammation and decreasing in cholesterol.

Notice that Phe TTC is reversed copy of leu CTT \leftrightarrow lysine AAA, AAG

And lys is the reversed copy of glutamate “GAA”.

Also, Phenylalanine synthesis encode leucine, while Lys synthesis encode Glu “GAA” synthesis too.

So both of lysine and phenylalanine are stabilizing each other and also stabilizing Leu and Glu functional activities in human.

The phenylalanine function is connected to lysine function and consequently contribute to lysosomal function and E coli, that phenylalanine has important role in promoting active proteins synthesis that as Phe proper function increased as reflect increasing in lysosomes and E coli proper function through promote encoding of lysine triplets which activate lysosome degradation function, that the presence of lysine phosphorylation on lysosomal surface will increase lysosome functionality on polymers digestion, followed by producing ATP-dependent peptide “poly-L-lysine” which promote Phe for producing chloramphenicolacetyl-transferase “CAT” in E coli yielding proteins.

That it's reported: phenylalanine addition increase the rate of active protein synthesis, and yield of chloramphenicolacetyl-transferase “CAT” expression in E. coli, indicated the highest expression rate was accompanied by the highest apparent rate of protein degradation (so lysosomal degradation which promoted by lysine is so important for activating phenylalanine functional which promote Cat synthesis in E. Coli necessary for cellular development pathways). [154]

So, as increasing in the lysine will contribute to increasing in ATPase production and increases the lysosomal digestive footprint, followed by increasing in E coli functions and then enhancing protein synthesis throughout including in Lys polypeptides and increasing in Phe polypeptides which regulated by phenylalanine/ hydroxylase for CAT synthesis in E coli that responsible for activating anti-endotoxin.

And, it has been reported: the poly-L-lysine-mediated the increased in the ATPase activities of HsIU, that appears to be responsible for the dramatic activation of the ATP-dependent peptide

hydrolysis by HslV. [155]

Also the lysine

And transmembrane lysine has Critical role in increasing the aminophospholipid transport by ATPase (which activated first by lysine phosphorylation on lysosomal surface followed by poly-L-lysine-mediated production which enhance Phe for CAT synthesis followed by active protein synthesis). [156]

The phenylalanine has critical role in amino phospholipids synthesis and transport as we described before,

That it has been reported that: the maximum velocity of rat liver phenylalanine hydroxylase is stimulated by the following phospholipids, in Order of decreasing potency: lysolecithin, lysophosphatidyl-Serine, phosphatidylserine, and sphingomyelin. Lysolecithin. [157]

The mechanism of maximum velocity of rat liver phenylalanine hydroxylase is stimulated by the phospholipids (which promoted by lysine) is done through activating ATPase and increasing the phospholipid transport function which mediated by both Lys acetylation and Phe hydroxylase productions, followed by encoding Glu which promote Phe hydroxylase followed by Tyr hydroxylase production which activate dopamine production.

Also studies reported that: Lys-rich-peptides and Phe-rich-peptides are having strong antimicrobial function and antioxidant function Among Lys10-substituted peptides, Pis-F1K/V10K and Pis-F2K/V10K, (with Lys substitution of Phe1 or Phe2, respectively) showed higher antibacterial activity than Pis-F6K/V10K, suggesting that Phe6 plays a key role in the antibacterial activity of Pis-1. [158]

And Piscidin-1-analogs with double L- and D-lysine residues exhibited different conformations in lipopolysaccharide but comparable anti-endotoxin activities. [159]

The, Antimicrobial peptides produced in E. coli are often expressed as fusion proteins which activate mitochondrial functions (started by lysine rich polypeptides, followed by ATP-dependent peptide synthesis, then followed by CAT production). [160]

So, lysine is strongly enhance Piscidin-1 (which contain a phenylalanine-rich amino-terminus) productive functions within E. coli (regulated by Phe) through activating lysosomal Functions mediated by CAT synthesis within E.coli. That the decreasing in lysine reflect decreasing in lysosomal digestive functions, followed by increasing in the accumulated polymers and cholesterol which promote calcification, followed by decreasing in Phe hydroxylase synthesis (phenylketonuria), and decreasing in antioxidant function, followed by decreasing in antimicrobial peptides function, and followed by increasing in accumulation of phenylalanine that can cause mutated disorders protein within cells.

12. Lysine has Strong Role in Activating Lysosomal Functions

Lysine has strong role in activating ATPase production which activate lysine phosphorylation in lysosomes, and activate both of lysine acetylation and Phe hydroxylase which activate E coli functions followed by activating Tyr hydroxylase and dopamine production.

Lysine AAA, AAG, <-encode -> Phe TTT, TTC, Where, lysine AAG is the reversed copy of glutamate Glu "GAA", that are having same functions for activating lysosomal activation and activating antihypertensive pathway (as discussed before).

The Lysine-selective molecular tweezers are cell penetrant and concentrate in lysosomes. [161]

And, the Lysine "AAA AAG" is a common determinant for mannose phosphorylation of lysosomal proteins. [162]

That lysine upon lysosomes digestion will activate ATPase which perform the main functional activities by lysosomes digestion and in E coli for activating Lys acetylation which activate and increase the phospholipids transport, and activate Phe/ hydroxylase production which carry strong roles in promoting Tyr/ hydroxylase productions which activate dopamine production.

That, Lysine-based Structure Responsible for Selective Mannose Phosphorylation of Cathepsin D and Cathepsin L Defines a Common Structural Motif for Lysosomal Enzyme targeting. [163]

And lysine fatty acylation promotes lysosomal "digestion" targeting the TNF- α . The result is an important first step toward understanding the biological functions of lysine fatty acylation. [164]

TEADs, which play essential roles in Organ development, are regulated by Phosphorylation of their coactivators,

YAP/TAZ. That TEADs Are long-chain fatty acylated at Conserved lysine residues too. [165]

Also it has been reported: LAAT-1 was required to reduce lysosomal cystine levels and suppress lysosome enlargement. [166]

Lysine is basic amino acid transporter (due to it encode Phe which connected with lysine for wide cellular effective functions) on the vacuole membrane. And the absence of lysine destabilizes purified Ypq1 and causes it to aggregate. [167]

The Lysine also bind with phosphatidylinositol 3,5-bisphosphate (PtdIns3,5P) through activating lysosome critically regulates trafficking and membrane dynamics (due to its connection with Phe function) by Direct Activation of Mucolipin Ca²⁺ Release Channels in the Endolysosome. [168]

It Is important for lysine-rich cluster 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 PKC α . [169]

Also, phenylalanine "TTT, TTC" is formed and stabilized by translation which done by lysine "AAA, AAG" which done after activating lysosomal phosphorylation, that Phenylalanine di-

gestion by lysosomes (lysine phosphorylation) for producing Phe/hydroxylase, and for building promoters within necessary RNAs and subunits (eg : amylase, trypsin and lipase) for producing Lys rich Peptides and Phe rich peptides (which approved are having antibacterial functions) and then for improving cellular and tissues functional pathways.

That it's reported that :Phe regulates the synthesis or secretion of α -amylase, trypsin and lipase through mRNA translation initiation factors – S6K1 and 4EBP1. [170].

The absence of lysine will be the result of lysosomal dysfunction and defect in lysosomal digestion, followed by decreasing in Phe hydroxylase production, and increasing in the accumulation of phenylalanine, and accumulation in un-digestive polymers that will cause phenylketonuria which characterized by defect in dopamine synthesis and increasing in calcification, with increasing in the risk of causing blood disorders, cardiac dysfunction, and increase the risk of pulmonary diseases.

As Phe accumulated as indicated the absence of Phe hydroxylase, and absence of lysine acetylation, and reflect the lysosomal dysfunction followed by decreasing in ATPase function and decreasing in E coli functions, followed by coronary calcification and Heart disease.

That it has been reported that: phenylalanine level of 900 μ M may be a threshold for congenital heart disease. [171]

That, Patients with Phenylketonuria (PKU) are exposed to multiple cardiovascular risk factors. [172]

Also, lysine has the antioxidant function,(as discussed before). [173] that the deficiency in lysine will cause lysosomal dysfunction and associated with both calcification and accumulated phenylalanine too.

And, Treatment with L-lysine seems to slow down the progression of diabetic nephropathy. [174]

And, phenylketonuria (which characterized by lysosomal dysfunction, as discussed before) associated with diabetes disease too. [175]

So lysosomal dysfunction associated with decreasing in ATPase followed by decreasing in Lys acetylation and decreasing in Phe/hydroxylase production (phenylketonuria), followed by accumulation in Phe and Associated with calcification in blood vessels.

And, the decreasing in lysine will cause lysosomal dysfunction followed by increasing in the accumulation of undigested polymers and cholesterol followed by accumulation of phenylalanine and followed by calcification and high risk of coronary disease, and high risk of tumor cancer depend on percentage of deficiency and percentage of lysosomal dysfunction.

That phenylketonuria patients, associated with greater melanoma risk. [176]

Also, And, decreasing in lysine reflect decreases in lysosomes function, followed by decreasing in NAADP and decreasing in antimicrobial production.

That it's reported PKU is a potential cause of tubulointerstitial disease associated with increased oxidative stress (due to decreasing in lysine and in adenine binding which necessary for NAADP production and necessary for antimicrobial synthesis in E coli). [177]

So it's clear that phenylketonuria due to sever decreasing in lysine "AAA, AAG" function followed by lysosomal dysfunction and deficiency In both of ATPase and in Lys acetylation production, which followed by decreasing in Phe/ hydroxylase, and reduction in dopamine production.

13. Lysosomal Dysfunction Reflect Decreasing in Lysine and Atpase Followed by Increasing in Tnfa and Decreasing in VEGF-A, Causing LV Hypertrophy and Cardiomyopathy

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. [178]

And, Cardiovascular Risk Associated With TNF Alpha Inhibitor Use in Patients With Rheumatoid Arthritis. [179]

Also, TNF- α blockade may improve insulin resistance and lipid profiles in patients with chronic inflammatory diseases. [180]

And, Elevation of Tumor Necrosis Factor- α and Increased Risk of Recurrent Coronary Events After Myocardial Infarction. [181]

Lysine as discussed previously activate lysosome through activating Firstly the ATPase which activate lysine phosphorylation on the lysosomal membrane that activate lysosomal digestive function, and activate E coli through Firstly activate lysine acetylation followed by activating Phe hydroxylase which activate E coli and dopamine production mediated by activating Tyr hydroxylase production, followed by activating NR4As pathway which promote Ang2-AT2 and VEGF-A synthesis.

As VEGF-A produced as TNFa reduced in vivo. Where, TNFa activate irregular proliferation which reflect the lysosomal damage.

In cardiomyopathy

Proinflammatory cytokines have been shown to be increased systemically or in the myocardium of subjects with heart failure. [182]

The increasing in TNFa never reflect benefits condition in vivo, but reflect down in anti-inflammatory processes and decreasing in both lysosomes and in E coli functions, that as discussed before the increasing in TNFa reflect increasing in undigested polymers and inflammation, and decreasing in VEGF-A production.

The Increasing in

Left ventricular. Size is due to the accumulation in the cholesterol and in undigested polymers which by itself activate TNFa and pro-

liferation in the Left ventricular.

Causes alterations of heart structure that affect function. An increase in left ventricular wall thickness (hypertrophy) causes left ventricular outflow obstruction, diastolic dysfunction, myocardial ischemia, and mitral régurgitation. [183]

And, the cardiomyopathy associated (with low Blood pressure) with hypotension due to decreasing in lysine with decreasing in both of lysosomes and ATPase production which produced by lysine (as described before)

That will be the result of decreasing in blood pressure (hypotension).

That it has been approved that:

The development of HCM is associated with hypotension. These results suggest that a decrease in blood pressure could be a biomarker signal for HCM leading to HF and early death. [184]

So positively, the cardiomyopathy caused due to lysosomal dysfunction followed by decreasing in atpase and in lysine acetylation followed by decreasing in Phe hydroxylase, followed by accumulation in undigested polymers which activate TNF α with increasing levels much more than VEGF-A, that will cause increasing in proliferation in vertical tissue cells caused increasing in LV hypertrophy.

That, Many LSD patients show very severe cardiac phenotypes, including hypertrophic and dilated cardiomyopathy, coronary artery disorders, and valvular defects. [185]

And, Despite significant increases in the left ventricular mass of hypertrophy animals, a normal balance of mitochondria and myofibrils was maintained within the myocardium. Further analysis indicated an enhanced lysosomal population in the hypertrophy group compared to the normal group. [186]

So it's clear that increasing in hypertrophy is related to decreasing in lysosomes functions (not related to mitochondria), and specifically connected to decreasing in atpase function which produced by lysine that necessary to activated proper lysosomal digestion through activating lysine phosphorylation and lysine acetylation which necessary to activate E coli functions.

And, Lysosomal dysfunction appear in diabetic cardiomyopathy. [187]

And positively, Lysine is the most effective amino acid for activating all of ATPase, GTPase, and lysosomes, and E coli functions, where ATPase necessary for activating lysine Phosphorylation for activating lysosome digestion, followed by activating E coli through activating Phe hydroxylase production, while GT-Pase necessary for activating mitochondrial repairs, which act on pro-inflammation and cholesterol for activating estrogen production and activating the NR4As pathway which activate all of Oxytocin, Nrf2 followed by Ang2-AT2 and VEGF-A production and

then followed by activating heme oxygenase and anti-inflammatory growth and processes, that prevent LV-hypertrophy, and prevent coronary calcification.

Heart failure (HF) is a syndrome of ventricular dysfunctional and great reduction in lysosomes and E coli functions followed by reduction in mitochondrial function, followed by reduction in NR4As functional pathway which reflect reduction in both of Ang2-AT2 and VEGF-A productive functions, followed by reduction in heme oxygenase and in anti-inflammatory growth which can be result of alterations in both systolic and Diastolic pressure , followed by increasing in TNF α production (with reduction in VEGF-A) which independent on cellular pathway .

Left ventricular (LV) dysfunction causes shortness of breath and fatigue, and cause dysfunction in right ventricular (RV) (that reflect reduction in ACE followed by reduction in VEGF-A and then reduction in heme oxygenase and reduction in anti-inflammatory function) , and cause peripheral and abdominal fluid accumulations .

The loss of ACE2 functions will be the result of decreasing in Ang2-AT2 followed by inhibition in VEGF-A synthesis followed by increasing in TNF α production , and can lead to HF.

That, Angiotensin II Stimulates Gene Expression of Cardiac Insulin-Like Growth Factor I.

[[Angiotensin II Stimulates Gene Expression of Cardiac Insulin-Like Growth Factor I and Its Receptor Through Effects on Blood Pressure and Food Intake

Marijke Brink, Jacqueline Chrast, S. Russ Price, William E. Mitch and Patrick Delafontaine

Originally published1 Nov 1999<https://doi.org/10.1161/01.HYP.34.5.1053>Hypertension. 1999;34:1053–1059]]

That Ang II (Ang2-AT2) significantly increase the production of mitochondrial H2O2 in vascular endothelial cells. [189]

Also , the inhibition in ACE2 (Ang2-AT2) reflect Inhibition in NR4As pathway that reflect Inhibition in GCs-beta followed by inhibition in B-arrestin and in B-adrenergic followed by inhibition in antioxidant (oxitocin and Nrf2 synthesis) production which followed by Inhibition in heme oxygenase and in anti-inflammatory growth , followed by cardiac dysfunction, where NR4As pathway necessary for adopting cardiac functions and constrictions .

That, the loss of ACE2 resulted in worsened cardiac dysfunction, cardiac hypertrophy, and fibrosis. [190]

And, AT2R has been revolutionized by the discovery of a direct agonist, C21, which promises to become part of the treatment of cardiovascular disease. [191]

And, it has been reported that: the diastolic LV function parameters were altered by angiotensin II. [192]

As we discussed before that lysine activate lysosomal Functions

and both of E coli and antioxidant via activating NR4As pathway, as the activating of antioxidative pathway as will protect from the LV hypertrophy.

That, Enhancing anti-oxidant gene expression may also prove to be a strategy for opposing cardiac hypertrophy [193]

It's so imp to note as as lysine AAA, AAG, promote ATPase and GTPase production as is able to reduce the LV hypertrophy that Extracellular Adenosine Attenuates Left Ventricular Hypertrophy Through Its Impact on the Protein Kinase and Phosphatase Interaction. [194]

As I mentioned previously, the lysine activate both ATPase and GTPase followed by activating both lysosomes and E coli mediated by Lys acetylation and Phe hydroxylase production, followed by activating dopamine and NR4As pathway which play important role in activating heme oxygenase and anti-inflammatory processes and growth .

The Loss of heme oxygenase 2 causes reduced expression of genes in cardiac muscle development and contractility, and leads to cardiomyopathy. [195]

The loose of HO-1 will reflect Inhibition in Ang2-AT2 and in VEGF-A productive functions, the the decreasing in Ang2-AT2 will decrease the Contractility of muscles lead to weakness in muscles.

Where cardiomyopathy is defined as the heart can't efficiently pump blood to the rest of your body, with shortness of breath or heart palpitations. [196]

And, the activating NR4As pathway can activate and adopt heart function mediated by adjusting the mitochondrial function [197]

14. ACE Activate both of Angiotensin-2 “Ang-2” and VEGF-A which Necessary for Promoting Heme Oxygenase and Reactivate Blood Flow

Lysine activate Lysosome and E coli followed by activating NR4As pathway which activate all of oxitocin, and Nrf2 followed by Ang2-AT2 and VEGF-A productive functions which necessary for modulation role blood pressure, and adjusting anti-inflammatory growth, followed by promoting heme oxygenase and increase blood flow.

Firstly: Angiotensin-2 play a modulatory role in blood pressure and imp for adjusting anti-inflammatory processes, and antiatherosclerotic and reactivate blood flow. [198]

And, IL17 activate glucocorticoid-beta synthesis followed by B-adrenergic productions which will activate Nrf2 synthesis for activating ACE for Ang-2 and VEGF-A synthesis for running adopted anti-inflammatory growth.. [199]

And, the vascular endothelial growth factor (VEGF) regulates HO-1 expression (through feedback) in vascular endothelial cells (ECs). [200]

That the ACE-Ang II-AT1 receptor axis cause the excess of ACE2-United Prime Publications., <https://clinicsofoncology.org/>

Ang-(1-7)-Mas receptor axis . [201]

Where Ang1-AT1 bind to ACE to induce ACE2-Ang-(1-7)-Mas receptor axis that considered as the Ang2-AT2 productions which then promote VEGF-A synthesis followed by heme oxygenase and enhancing anti-inflammatory pathways .

The Ang II production (Ang2 Tie2 or Ang2-AT2) has the roles of activating VEGF-Ang-Tie2 which responsible for activating heme oxygenase and anti-inflammatory growth.

And, Ang II

Mediated signals are transmitted and involved in the VEGF-Ang-Tie2 synthesis via Heparin-EGF-mediated EGFR (HB-EGF) trans-activation, where that link should be considerable in pathological conditions in which collateral blood flow is required. [202]

So, ACE promote Ang2-AT2 (ACE2-Ang2 AT2) which promote VEGF-A synthesis followed by enhancing heme oxygenase and anti-inflammatory growth that could be the result of increasing in blood flow .

And then blocking ACE functions will inhibit Ang2-AT2 production and VEGF-A synthesis followed by inhibition to heme oxygenase (which originally activated by oxitocin followed by Nrf2 production), followed by ventricular dysfunction and cardiac hypertrophy depend on the percentage of ACE inhibition and percentage of increasing in NFκB activities for increasing the uncontrolled cellular growth (which promote tumor survival).

Also, the destruction of insulin-producing beta cells in the pancreas is the main reasons for type-2 diabetes , where activating beta-cell reflect the the Ace activation for producing 2-Ang1-Ang-2 (Ang2-AT2) which necessary to activate VEGF-A synthesis followed by activating heme oxygenase and anti-inflammatory growth and functions.

But, involving the leucine glycine in beta cells will prevent its construction by T-cells, and will activate oxitocin and Nrf2 followed by activating ACE functions which activate antioxidant and prevent diabetes by activating Ang2-AT2 synthesis followed by VEGF-A production , that also associated by reduction in NFκB synthase and increasing in both heme oxygenase and in anti-inflammatory growth. [203]

So, the absence of leucine (which activated by Glu “GAA” which is reversed copy of Lys “AAG”) and glycine will prevent the activation of OPA1 (where leucine enhance both oxitocin and Nrf2 production and enhance mitochondrial activation), and prevent the production of antioxidant which followed by inhibition to VEGF-A by Inhibition in ACE functions and mediated by inhibition to Ang2-AT2 productions.

Also, réduction in Leu and glycine will activate the high doses of TNF-induce apoptosis due to the accumulation of cholesterol and inflammatory Caspases (inflammatory Caspases are accumulated due to the damage in the mitochondrial OPA1 membrane which necessary for activating B cells repair and growth) .

That Caspases not only play an essential role during apoptotic cell death, but inflammatory caspases—are associated with immune responses to microbial pathogens. [204]

And, it's reported that data demonstrate TNF- α promotes FasL expression through NFAT activation in neuroblastoma cells. [205]

15. Lysine Adopt Hypertension, Antioxidant, and Treat Blood Disorder through Activating Lysosome & NR4As Pathway

The Lysine supplementation resulted in normalization/reduction of blood pressure of hypertensive subjects who have suboptimal lysine intake. [206]

Lysine is an Lp(a)-binding inhibitor acts as antioxidant.

That it has been reported that Lysine harvesting is an antioxidant strategy and triggers underground polyamine metabolism. [207]

And, the Accelerated lysine metabolism conveys kidney protection. [208]

That the digestion of polymers and cholesterol by lysosome will enhance full protection to kidney from polymers toxicity and damages.

Also, Lysosomal dysfunction and altered activities of lysosomal cathepsins have been observed in the diabetic heart. [209]

Also, Lysine functions slow down diabetic nephropathy

Through activating E coli and mitochondrial function followed by activating dopamine followed by activating estrogen and GC-beta through activating NR4As pathway which activate oxitocin and Nrf2 production.

Where, Treatment with L-lysine seems to slow down the progression of diabetic nephropathy. [210]

And, Lysine exerts a clear antioxidant effect on soybean oil, and is potential antioxidant for use in lipidic foods, and also lysine reduce the The amount of toxic aldehydes. [211]

16. Lysine Enhance Cardiac Function and Protect From Pulmonary Disease

Lysine necessary for blood synthesis, And hemoglobin is known to contain lysine, hence a lysine deficiency would prevent hemoglobin synthesis. Also, the heme group itself must be synthesized, presumably from amino acids, and lysine may be the precursor.

Lysine necessary for activating blood platelet function. [212]

Lysine play imp role in activation lysosomal function and blood platelets functions , that as lysosomal dysfunction begin as Lys deficiency will be followed by anemia.

Nuclear ATR lysine-tyrosylation protects against heart failure by activating DNA damage response.[213]

Lysine protect from pulmonary disease, that L-Lysine protects against sepsis-induced chronic lung injury in male albino rats. [214]

L-Lysine Decreases Nitric Oxide Production and Increases Vascular Resistance in Lungs Isolated from Lipopolysaccharide-Treated Neonatal Pigs.. [215]

And Poly-l-Lysine Compacts DNA, Kills Bacteria, and Improves Protease Inhibition in Cystic Fibrosis Sputum. [216]

Also it's reported that L-lysine treatment under certain conditions could sustain cardiac performance. .[217]

Phenylalanine enhance antioxidant, immunity, and dopamine function for improving depressed myocardial function following acute coronary arterial embolization:

Phenylalanine Plays Important Roles in Regulating the Capacity of Intestinal Immunity, Antioxidants and Apoptosis in Largemouth Bass.[218]

Phenylalanine and tyrosine constitute the two initial steps in the biosynthesis of dopamine, which, in its turn, is the metabolic precursor of noradrenaline and adrenaline.[219]

Dopamine is a neurotransmitter that is produced in the substantia nigra, ventral tegmental area, and hypothalamus of the brain.

Dopamine increased pulse pressure, heart rate and circulating epinephrine ϵ and norepinephrine (NE) levels. [220]

And, It is concluded that dopamine will improve depressed myocardial function following acute coronary arterial embolization, at least temporarily. [221]

Dopamine increase antioxidants function. That Dopamine has stronger antioxidant activity than other related compounds that is correlated to the numbers of hydroxy groups on the phenolic ring. [222]

Notice Brain Disorders Due to Lysosomal Dysfunction (which reflect reduction in lysine acetylation and in both Phe hydroxylase and Tyr hydroxylase) . [223]

While Dopamine (DA) plays a vital role in reward and movement regulation in the brain. [224]

17. Phenylketonuria

Phenylketonuria is the accumulation of phenylalanine due to absence of lysine which necessary to activate ATPase and both of lysine acetylation and Phe/ hydroxylase:

Lys AAA, AAG \leftrightarrow Phe TTT, TTC

(PKU) is caused by defective activity of phenylalanine hydroxylase (PAH), the enzyme that converts phenylalanine (Phe) to tyrosine. Toxic accumulation of phenylalanine and its metabolites, left untreated, affects brain development and function depending on the timing of exposure to elevated levels. [225]

Phenylketonuria associated with lysosomal enlargement.

Fabry disease (FD) is an X-linked lysosomal storage disorder due to a deficiency of the enzyme alpha-galactosidase A.

The first report of co-existence of FD and PKU, two different congenital inborn of metabolism and in consideration of the prev-

absence of each disease this chance association is a very unusual event. [226]

Phenylketonuria (PKU), is an inherited autosomal recessive disorder caused by a deficiency in phenylalanine hydroxylase (PAH) or one of several enzymes mediating biosynthesis or regeneration of the PAH cofactor tetrahydrobiopterin. [227]

Actually Phe increase the function of cell membrane permeability (but in the availability of proper lysine and lysosomal functions) which is so important for cells vitality and function in relation and connected to lysine function in lysosomal surface, but in lysosomal dysfunction and absence of lysine will reduce or inhibit the Phe functional stability that will reduce Phe hydroxylase productions and reduce dopamine production followed by phenylketonuria.

18. Lysosome Control Both of Dendritic Cells and MHC Class 1 & 2, that Promote Contribute to Myocardial Protection

Both lysine and Phe are so necessary to contribute to myocardial protection through proper activation to lysosomes and E coli functions (as discussed before) that followed by activating all of Lys methylation, Phe/ hydroxylase, Tyr/ hydroxylase, and dopamine, followed by activating mitochondrial function (by producing GTPase) followed by estrogen synthesis, and MHC 1 MHC 2 production (formed from cholesterol and from undigested polymers) respectively, followed by activating NR4As pathway (which regulated by valorphin) for producing oxytocin and Nrf2.

That it has been approved that, Lysosomes control of dendritic cell function. [228]

Also, it has been approved that: MHC Class II Presentation Is Controlled by the Lysosomal Small GTPase. [229]

Dendritic cells and B cells are also APCs expressing MHC class II. CD4+ T cells recognize antigens presented on macrophages by using TCR. [230]

B-Cells are highlighted as playing a prominent role in its progression, regardless of aetiology, through mechanisms that are dependent and independent of antibody production. These mechanisms include secretion of pro-inflammatory cytokines, monocyte recruitment following myocardial injury, and interaction with CD4+ T helper cells, with a subsequent amplification of the inflammatory cytokines, monocyte recruitment following myocardial injury, 65 and interaction with CD4+ T helper cells. [231]

And, B cell subsets contribute to myocardial protection by inducing neutrophil apoptosis after ischemia and reperfusion. [232]

And it has been reported that: B-cells might have potential applications in treating cardiovascular diseases. [233]

So, it's clear that GTPase which produced by lysine (AAA, AAG) control dendritic cell function (by activating mitochondria), and control MHC Class II Presentation (which produced by B cells),

that contribute to myocardial protection via activating antihypertensive pathway and NR4As pathway.

And lysosomes activate B cells through lysine functions pathway which produce both ATPase and GTPase for activating mitochondrial fusion and functions, and Class II Presentation following heart injury.

19. Valorphin can Reactivate E Coli, Hence will Reactivate Lysosome by Translation for Lysine Production

Valorphin (known as VV-hemorphin-5) is nine essential amino acids:

Leu_Val_Val_Tyr,_Pro_Pro_Thr_Gln_& Arg

Necessary for immune functions. [234,235]

As mentioned before that Glu *GAA" is the reversed copy of Lys "AAG" and at the same time can enhance Leu "CTT" synthesis,

That both of Lysine AAG and Glu GAA can reactivate ATPase, and GTPase, which enhance lysosomes and E coli functions followed by contributing to myocardial protection (as mentioned previously).

That

Lys AAG <--> GAA Glu <--> CTT Leu

As both of Lys can activate both of Glu and Leu synthesis, as

Indicated that lysine has important role for activating valorphin through activating Glu and Leu, that all of those three amino acids are necessary to activate mitochondria and lysosomes phosphorylation digestive functions, followed by activating E coli and dopamine synthesis, followed by activating NR4As pathway for activating antioxidants, heme oxygenase, and full anti-inflammatory processes that prevent calcification and prevent coronary artery disease, followed by increasing in neuroprotective effects on hypoxic motor neuro, and increasing in the protection against memory impairment.

20. Conclusion

The lysosomal dysfunction promise accumulated phenylalanine, inflammation, and cholesterol deposit in arteries walls and exert calcification because of the accumulation of undigested polymers which included cholesterol and pro-inflammation.

The lysosomal dysfunction caused accumulation of the undigested inflammation, polymers, and accumulation of cellular waste, that also reflect the cholesterol accumulation.

Lysosome dysfunction contributes to cardiovascular disorders, neurodegenerative diseases, coronary calcification, and atherogenesis.

Lysine has strong role in activating ATPase production which activate lysine phosphorylation in lysosomes, and activate both of lysine acetylation and Phe hydroxylase which activate E coli functions followed by activating Tyr hydroxylase and dopamine production.

Lysine AAA, AAG, <−encode −> Phe TTT, TTC,

Where, 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).

Phenylalanine “TTT, TTC” is formed and stabilized by translation which done by lysine “AAA, AAG” which done after activating lysosomal phosphorylation, that Phenylalanine digestion by lysosomes (lysine phosphorylation) for producing Phe/ hydroxylase, and for building promoters within necessary RNAs and subunits (eg : amylase, trypsin and lipase) for producing Lys rich Peptides and Phe rich peptides (which approved are having antibacterial functions) and then for improving cellular and tissues functional pathways.

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

The absence of lysine will be the result of lysosomal dysfunction and defect in lysosomal digestion, followed by decreasing in Phe hydroxylase production, and increasing in the accumulation of phenylalanine, and accumulation in un-digestive polymers that will cause phenylketonuria which characterized by defect in dopamine synthesis and increasing in calcification, with increasing in the risk of causing blood disorders, cardiac dysfunction, and increase the risk of pulmonary diseases.

The cardiomyopathy associated (with low Blood pressure) with hypotension due to decreasing in lysine (which responsible to activate both ATPase and GTPase), decreasing in both of lysosomes and E coli followed by decreasing in blood pressure (hypotension), followed by reduction in VEGF-A, and then followed by increasing in TNF α which responsible for increasing in LV hypertrophy.

If we want to talk and discuss about lysine, we must link our discussion to the strength of the activity of phenylalanine, which is linked to the strength of the activity of lysine, as those two amino acids are linked to each other in vivo, where we consider that lysine functions are the main activator to phenylalanine functional pathway as described before.

It's clear that GTPase which produced by lysine (AAA, AAG) control Dendritic cell function (by activating mitochondria), and control MHC Class II Presentation (which produced by B cells), that contribute to myocardial protection via activating antihypertensive pathway and NR4As pathway.

And lysosomes activate B cells through lysine functions pathway which produce both ATPase and GTPase for activating mitochondrial fusion and functions, and Class II Presentation following heart injury.

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