Research Article

Pyrimidine within Tyrosine kinase and other (PSTGk, PSTCk, PSTAk) kinases produced from mTOR-FOX binding through effects of Ser/Thr phosphorylation mechanism play necessary rules for removing insulin resistance, and tumors.

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The purpose of this study is:

Studying the Ser/Thr phosphorylation mechanism effects on mammalian target of Rapamycin FOX binding mechanism pathways for removing insulin resistance and recover tumor cancer cells and understanding that pyrimidine (Thymine, Cytosine) are playing imp rules in tumor cells cancers recoveries, and the Ser /Thr amino acids are the Phosphorylation regulators tools effects on pro-mTOR bind to FOX genes for producing the four kinds of protein kinases, for S6K1 genes synthesis, for ribosomal p70S6 kinase reactivations, and insulin productions.

Abstract

MTOR genes are originated and activated from ribosomal genes S6K1 and p70S6 with mitochondrial contributions. mTOR pathway is considered a necessary tool for regulating and activating necessary cellular pathways by which eukaryotic cells adjust their protein biosynthetic capacity for nutrients needs and availability.

The necessary phosphorylation processes on pro-mTOR protein lead to the production of four kinds of protein kinases for running and regulating most of cellular metabolism and for blood circulation. the G-protein kinase and GTPase synthesis will contribute most of cellular and genes activities throughout the binding of pro-mTOR with FOX forkhead genes for production of the four kinds of protein kinases and for increasing the FOX stabilities, that will lead to sestrin-Leu-1 synthesis, S6K1 genes production, and cholesterol production. During the binding of mTOR with FOX genes, the resynthesis of necessary hydrophobic amino acids will be done with the contribution of mitochondrial enzymes and GTPase, then, the PSTG, PSTC, PSTT, and PSTA Protein kinases will be produced with the productions of PTEN protein and S6K1 genes.

The mTORC1 will be formed from PSTC Protein Kinases for tRNAs, for autophagy productions and for regulating the mTORC2 synthesis. The increasing of AMPK activities will be for the Akt synthesis priority by attracting and using phosphorylation processes for Akt synthesis from PSTG protein kinase then for GTPase pathways productions.

Cardiac arrest is due to increasing in ATPase with severe reductions in G-protein kinase and GTPase productions and increasing in +ve molecules in genes inside cells that will lead to an increase in cells sizes that will lead to precipitation of protein molecules in blood vessels due to decreasing in blood vessels permeability area regards to its normal sizes, that will lead to sudden cardiac arrest depending on the number of precipitated molecules and on the decreasing in arteries cylindrical sizes, means that your heart can suddenly stop beating in case of G-protein kinase reduction and reductions in GTPase resynthesis.

This cuts off blood flow to the brain and other organs. It's an emergency and is deadly if not treated immediately through re-increasing. GTPase and G-protein kinase with tyrosine kinase proteins, where GTPase with proper sequences are so necessary for Endosome and Golgi transport. Where GAPs coexist in most cells, that responsible for increasing the diversity of signals that regulate internal and external cellular pathways cycles.

The decrease in Akt molecules which are derived and synthesized mainly from G-protein kinase "PSTG" (and tyrosine kinases) with increasing in +ve molecules in the same protein can help the heart restart its activities.

Also, increasing +ve bonding energy & its positive molecular binding energy in any of the four kinds of protein kinase produced from pro-mTOR can lead to decreasing in their main active pathways and can be the main reason for heart disease problems.

Insulin resistance is due to decreasing or inhibition in the tyrosine kinase productions and pathways activities, and may associated with mitochondrial dysfunction too, which can show increasing in PSTA protein kinase productions and its pathways activities with reduction or inhibition in tyrosine "PSTT" protein kinase productions and pathways activities.

Materials

pro-Mammalian rapamycin bind with nutrients molecules (pro-mTOR)

_, G-protein kinase (PSTGk) , tyrosine kinase (PSTTk) , Cytosine kinases (PSTCk) , adenosine protein kinase (PSTAk)

_ mammalian Target of rapamycin complex subunit MLST8,

_hydrophobic amino acids, and Ser/Thr amino acids,

_Proto-oncogene, serine/threonine kinase PIM1

_mammalian target of rapamycin complex 1 and 2 (mTORC1, &mTORC2)protein kinases , Akt active proteins kinases , adenosine protein kinase, tyrosine (Thymine S/T kinases) active protein kinase,

_phosphatidylinositide 3-kinase (PI3K)

_inner cells chromosomal 13q14 gene,

_lysosomal security granules, and mitochondrial effective synthetase enzyme,

_inner ribosomal p70S6 genes

_eukaryotic initiation factor 4E binding protein 1 (4E-BP1),

_70-kDa ribosomal protein S6 kinase (S6K1)

_FOX forkhead genes

_ROR alpha genes

_GTPase genes

_ATPase phosphorylation tool

_cholesterol productions regulated by FOX and ROR alpha genes

_ insulin regulated and produced by pro-mTOR _FOX binding mechanism pathways

_enkephalin Leu-pentapeptides and Meth-pentapeptideactive genes

Introduction

The mammalian-target-of-rapamycin (mTOR) is multidomain protein kinases that are so important in regulating several cellular metabolic pathways including translational machinery.

mTOR complex 1 (mTORC1) and 2 (mTORC2), has a fundamental role in coordinating anabolic and catabolic processes in response to growth factors and nutrients **(**1**)**.

Mammalian target of rapamycin (mTOR) protein pathways is activated by specific amino acids, by insulin, and by growth factors.

When insulin digest its cholesterol substrate (which regulated by ROR alpha genes and by FOX transcription factor genes), the mTOR protein will be reactivated again through ribosomal p70S6 +S6K1

genes translations activities with mitochondrial inner membrane functions with the contraction of GTPase regulations functions for re-running regular mTOR biological cycles for normal insulin growth, for reactivating and repair the mitochondrial membrane, for pyrimidine resynthesis, for the rebuilding tyrosine leucine and other hydrophobic amino acids for estrogen and insulin synthesis, for rebuilding sestrin-Leu 1 genes through binding with FOX forkhead genes, and for re stabilizing FOX forkhead active genes with ROR-alpha genes.

mTOR acts as a 'master switch' of cellular anabolic processes and energy-producing catabolic activities including energy-intensive.

It promotes cells and hormone growth in response to extracellular mitogen, energy, nutrient and stress signals but depending on the availabilities of AMPK protein and phosphorylations tools and mechanism by ribosomes and other actin ATPase tools.

mTOR functions within two distinct complexes mTORC1 & mTORC2, where, mTORC1 is considered involved in the regulation of the translations initiating machinery influencing cell growth including proliferation, while mTORC2 participates in actin cytoskeleton rearrangements and cell survival under regulation by mTORC1. MTORC2 is a complex formed by translations from mTORC1 which are regulated by FOX genes box stabilities and activities and from ROR-alpha genes activities too.

MTORC2 can be considered as a stored emergency complex and feedback process for recover mTORC1, for reactivating autophagy, and for performing signals messages through the availabilities of lysosomal security granules which is necessary for activating autophagy.

MTOR complexes also considered as a synthesized protein kinase started from phosphorylation effects on pro-mTOR which originally produced from ribosomal genes or specifically subunits that will carry specific arranged sequences (have specific signals functions for ribosomes activities in several tissues) from ribosomal and mainly from 1st DNA strand and then will be modified and activated by mitochondrial membrane functions, then will follow the necessary cellular metabolic pathways.

MLST8 is the Target of rapamycin complex subunit LST8, also known as G protein beta that can activate mTOR by the reactivities of GTPase and AMPK protein pathways.

RHEB is also known as Ras homolog enriched in the brain (RHEB) is a GTP-binding protein that is ubiquitously expressed in humans depending on the availabilities of G-protein kinase, which normally is involved in the mTOR protein for the regulation and reactivate G-protein kinase synthesis for brain functions and for reactivating cellular metabolic depending cycles.

Activated FOXO-mediated insulin resistance is blocked by reduction of TOR activity, indicating pro-mTOR produces tyrosine kinase and G-protein kinase that should involve FOX forkhead stabilities and function for cholesterol synthesis for new insulin production and inhibit old insulin-like productions. **(**2**)**.

mTORC1 inhibition, (in addition to reducing protein synthesis), deeply affects gene transcription and initiates autophagy 07, where indicates that the active mTORC1 can contribute to cell stress.

Through the binding mechanism of mTOR to FOX for purifying its composition for generating the four necessary active proteins kinases: G-protein kinase (PSTGk), tyrosine kinase (PSTTk), adenosine protein kinase (PSTAk), and Cytosine protein kinases (PSTC K), those kinases will follow metabolic pathways for genes and alpha subunits productions, for ATPase and GTPase productions, for antigen reactivations, and for cholesterol productions which will be the substrate for estrogen and insulin growth and productions.

Through the binding mechanism of mTOR to FOX for purifying its composition for generating the four active proteins kinases, the Sestrins-Leu 1 will be produced, the adjusting of blood purines will be started by the mitochondrial synthetase and synthases enzymes by converting extra purines nucleotides to active pyrimidine nucleotides for reactivating the necessary hydrophobic amino acids and other necessary amino acids as Ser /Thr synthesis, and the limited ribosomal ATPase will be activated depending on the quality and quantity of the three kinases PSTGk, PSTT& PSTAk productions from the main pro-mTOR protein, then the GTPase will be activated for reactivating mitochondrial inner membrane and for its necessary pathways regulating activities.

The G-protein kinase pathways have the priority of using phosphorylation tools and kits instead of mTORC1 synthesis pathways where (PSTG) Kinase metabolic pathways have the priority in the metabolic process than other Cytosine kinases pathways, where can lead to delaying (but not inhibition) the Cytosine protein (PSTC) kinase pathways which needed for the mTORC1 production and the autophagy productions.

The increase in G-protein kinase activities will reflect the reductions in the tissue stress with increasing in sestrin-Leu 1 production, and increasing in adjusting the purines and branched fatty acids by mitochondria and contribution of some other genes and alpha subunits through the conversion of extra purines to pyrimidine nucleotides for building necessary amino acids for kinases protein synthesis and activities in the necessary cellular metabolic pathways and necessary genes signal activities through interstitium tissue fluid to several tissues.

The MTORC2 involved in cells proliferation and survival, cell migration and cytoskeletal remodeling which modulated by mTORC1 (with the modulation of PSTTk, and PSTGk), which indicated that the presence and protection of mTORC2 are so imp for autophagy activities but with modulations of PSTCK, PSTTK, and PSTG kinases active protein.

The mTORC2 complex consisting of seven protein subunits, that, rictor Gene, is necessary for ribosome binding and has the activity of protein kinase binding and found only in mTORC2 **(**3,4**)**. It has been considered that the scaffold protein is substrate binding to mTORC2, which indicates the necessity of mTORC2 for autophagy activities and regulations.

In another hand, mTORC1 considered being the modulator and regulator subunits for mTORC2 complex, that if reduced or inhibited will lead to free mTORC2 from mTORC1 modulations or mainly will be free from ribosomal S6K1 and from p70S6 genes modulations and necessary activities, that autophagy can be activated under modulations of other foreign genes (as toxic viral protease or other toxic factors), that autophagy will be activated irregularly without being regulated or modulating by original inner cells as inner ribosomal necessary genes (as active p70S6 ribosomal genes) , and without regulation by serine/threonine-Cytosine

Kinases Proteins (PS/TCK) Proteins that modulate the mTORC1 synthesis will not be repaired again or will not be monitored.

The inhibition of mTORC1 due to deficiency in pyrimidine active nucleotides or due to deficiency in hydrophobic amino acids will reflect the beginning and early decreasing in the specificity of autophagy to its living cells cellular cycles protection, and reflect the decreasing in autophagies belongisties and specificities to their original living cells, and can reflect early decreasing in sestrin-Leu 1 reactivities, with decreasing in FOX forkhead genes stabilities and inhibition in its imp regulations for cells proliferation survival, and migrations, and cytoskeletal remodeling pathways.

The active mTORC1 kinase protein which depends on the presence of active cytosines nucleotides and active hydrophobic amino acids with the availabilities of the presence of Serine and threonine amino acids that has its necessary regulations processes for cellular metabolism activities, and originated from the Pro-mTOR due to phosphorylations processes to produce the four kinases proteins in response to signaling pathways (where, signaling pathways can start by brain enkephalin pentapeptides activities, or with G-actin and its ATPase activities), and will be de-regulated in many human diseases where there were sever decreasing in Pro-mTOR-FOX binding activities pathways for cellular activities, and there was a severe deficiency in one or more of protein kinases productions specifically in PSTT, PSTG and in PSTC kinases Proteins.

Pro-mTOR protein metabolic pathways can be reactivated by phosphorylation processes by using the mechanism of Phosphorylation of serine/threonine amino acids in the mTOR protein chain for the productions of the necessary four kinds of protein kinases.

The serine/threonine-protein kinase PIM-2 (one of three PIM kinases) indicated its necessary functions for autophagy activities that are involved in its regulations, which was initially discovered as a regulator of glycogen synthesis and has also been found to be involved in autophagy modulations **(**5**)**.

Where, PIM serine/threonine kinases can be considered as active subunits sequences involved in the four kinds of protein kinases specifically in PSTC, PSTT, and PSTG Kinases Proteins for increasing their activities due to phosphorylation processes during the binding with FOX genes and play an important role in healthy cellular metabolic pathways as in anti-inflammatory processes, and in ribosomal genes resynthesis. That protein ser/Thr (PST) kinases can increase the modification of increasing of specific substrates including several cellular regulators and apoptosis mediators.

PIM1 but not PIM2 can increase the migration of normal and malignant hematopoietic cells by regulating chemokine receptor surface expression where PIM1 is the main regulator but PIM2 is the tool for PIM1 regulations as mTORC2 is the tool for mTORC1 regulations activities.

Proto-oncogene, serine/threonine kinase PIM1 is the products from Phosphorylation used the ser/Thr mechanism during the binding of pro-mTOR mTOR with FOX forkhead genes, where PIM genes is holding and monopolies the main amino acids and arranged sequence for running the phosphorylation mechanisms for producing the four kinds of protein kinases.

The PIM is the key to contributing to the formation of four proteins kinases, that each of sre/Thr (Ser:TCT, TCC, TCA, TCG /Thr: ACT, ACC, ACA, ACG) contain its specific triplets, where only Ser contains the Thymine nucleotides but not threonine, where deficiency in Ser will reflect a deficiency in Thymine nucleotides metabolic pathways, and thus will force cellular cycles to use threonine phosphorylation mechanism in case of its availabilities in cellular metabolic pathways.

Each of those produced active protein kinases will begin with a specific nucleotide at the beginning of its protein sequences chain that will characterize its functions and specificities in cellular pathways activities and will characterize the main variations between those protein kinases within pathways functions.

The main involvement of those two amino acids of Ser and Thr in most of the phosphorylation mechanisms of proteins regulations is the containing of Cytosine in the middle of their triplets that will

facilitate the binding of cytosine to phosphorus then release adenosine, Thymine, and guanine upon phosphorylation effects on pro-mTOR proteins, where at the Phosphorylation effects will act on Cytosine bind to phosphorus to release the other nucleotides for the production of the four kinds of protein kinase:

1) G-protein kinase (PSTG Kinase)

2) adenosine kinase PSTA Kinase which will activate ATPase cycles that will begin with adenosine nucleotides,

3) Tyrosine kinases (PSTT Kinase) which will activate Leu (TTG Or TTC) and other hydrophobic amino acids including tyrosine with some other necessary amino acids (depends on the presence of Thymine nucleotide in their triplets eg: PRO (TCC), Cys (TGT), Tyr (TAC or TAT), Arg (CGT), Ser (TCT or TCC or TCA), Gly (TGG), Asp (TAG), Ala (TCG), Val, (TTG), Ser (TGA), Asn (TAA), Tyr (TCA), Île (TTA), His (TAC),

4) The Cytosine kinases (PSTC Kinase) that can produce mTORC1 which can activate tRNAs and autophagy that their activities depend on the presence of cytosine nucleotides in the composition of their genes which necessary for migration functions.

Notice, may one or more of those protein kinases can be produced more than others depending on the quantity and quality of nutritions molecules and depending on the produced enzymes and active genes by chromosome and regulated by the ribosome, by mitochondria, and by the stabilities of both ROR alpha genes and FOX genes, that may have more threonine (ACA or ACG) than Ser (containing Thymine), that will produce more adenosine kinase with a deficiency in tyrosine kinase and in cytosine kinases that will reflect a problem in cellular metabolic pathways as breast cancer and maybe the main for capillaries blockage and Narrowing of the aorta, atherosclerosis, and failure in functioning branched fatty acids.

The production of tyrosine-protein kinase PSTTk due to phosphorylation on pro-mTOR protein will be derived for regulating specific cellular activities, where PSTT is necessary for leucine synthesis re-activities in several cellular pathways and for reactivating enkephalin Leu pentapeptides activity in the brain, and can be the regulating tools for antigen re-synthesis, and will be necessary with Leucine amino acids for regulating sestrin-Leu 1 synthesis during FOX genes binding regulation. Some of the produced nucleotides from amino acids due to Phosphorylation can be so necessary for protein synthesis, for enzyme productions, and for gene synthesis.

The G-protein kinase (PSTG) can activate ribosome and mitochondrial inner membrane through GTPase regulations, also G-protein kinase will be the stimulator for insulin secretion and productions, that the mitochondrial GTP (mtGTP) synthesized by succinyl-CoA synthetase (SCS) is hydrolyzed via mitochondrial PEPCK (PEPCK-M) to make phosphoenolpyruvate, a high-energy metabolite that integrates TCA cycling and anaplerosis with glucose-stimulated insulin secretion **(**6**)**

The role of PSTGk, PSTTk, and PSTCK in modulating mTORC1 production is for modulating and regulating tRNA too, and for regulating mTORC2 productions for tRNAs and for autophagy synthesis and reactivities, where phosphatidylinositide 3-kinase (PI3K) and mTOR complex 2 (mTORC2) are acutely activated by aa-readdition in a mTORC1-independent manner **(**7**)**.

The mammalian target of rapamycin mTOR, plays a critical role in maintaining a balance between cellular anabolism and catabolism throughout phosphorylation mechanism processes, through the binding mechanism to FOX forkhead genes, and through the effect of mitochondrial enzymes productions on pro-mTOR protein.

Where, the FOX-mTOR binding processes is necessary for the kinases protein productions, for sestrin-Leu 1 productions due to phosphorylations Ser/Thr mechanisms, for AMPK production, and then for mTORC1 production which regulate mTORC2 productions for autophagy and for tRNAs reactivation.

FOX gene subgroups transcriptional disturbances affecting numerous complex molecular cascades, and have been linked to a wide range of cancer, that indicate the importance of re-stabilities of FOX forkhead genes by the phosphorylations binding mechanism to pro-mTOR with the regulations of ribosomes and mitochondria for producing the four kinds of protein kinases which are so necessary for modulating and running cellular metabolic pathways.

The pathogenesis of colorectal cancer (CRC) is especially due to a deficiency in necessary nucleotides responsible for G-protein and for PSTA protein kinases production, where deficiency in Thymine, Cytosine nucleotides and in hydrophobic amino acids with a deficiency in Ser amino acids will show genomic instability, chromosomal aberrations, and DNA promoter hypermethylation. CIN tumors (are found on the surface of the cervix, and are usually caused by certain types of human papillomavirus {HPV}) show chromosomal gains and losses and structural rearrangement **(**8**)**.

CIN tumors indicate the origin of irregularities in Ribosomal ATPase molecular composition due to deficiency in Ser amino acids in the Ser/Thr phosphorylation mechanism, then consequently will reflect a deficiency in one or more of protein kinases productions, where are necessary for reactivating ribosomes and mitochondria inner membrane. The CIN reflect a specific mutation in the

rRNAs due to the deficiency in Thymine and or Cytosine nucleotides (depending on the cases and types of the missed amino acids) that reflect a deficiency in FOX genes stabilities and functions, and deficiency in protein kinases production which are necessary for ribosome mitochondrial inner membrane repair and stimulations, and are necessary for FOX forkhead genes stabilities and functions for regulating sestrin-Leu 1 synthesis, for cholesterol productions, for S6K1 productions, and for reactivating AMPK protein.

Colorectal cancer can start with a blockage in capillaries leads to isolation to specific intestinal cells with a deficiency in one or more hydrophobic amino acids and in protein kinases produced by phosphorylation on pro-mTOR, which can lead to inflammation in goblet cells. Decreasing in the PSTG with PSTA Kinases protein can lead to a reduction in ATPase production and in GTPase activities that lead to mutations in rRNAs which can be spread.

The deficiency in mTORC1 regulation activities will reflect a reduction in the migration of protein molecules lead to tumor. The reduction in GTPase activities will lead to increasing in cell size and decreasing in ribosome activities where GTPase are needed for modulating most of the cellular metabolic pathways, that the PSTG Kinase pathways have the priority for using the Ser/Thr phosphorylation mechanism for Akt production and for modulating the GTPase activities. mTOR signaling is activated indirectly by hormones and growth stimulated factors, where signals are negative charges started by ribosomes and by G-actin negative ATPase small subunits to be sent through inner cells to start mTOR synthesis that will carry all cells needs throughout its created protein sequences that will be derived to the bloodstream to reconnect and united with nutrition absorbed molecules and rebind with FOX forkhead genes for reforming the for kind of protein kinases.

cholesterol synthesis is regulated by FOX and ROR alpha genes through the production of PSTA, PSTG, PSTC, and PSTT kinases protein during phosphorylation Ser/Thr mechanism on mTOR, and the AMPK is activated during the same metabolic cycles for running the full active cellular pathways, where at time of decreasing in insulin the cholesterol which is its substance will be synthesis to reactivate insulin growth, where mTOR can be stimulated and affected by the PI3-kinase pathway and PKB/Akt **(**9**)**.

During FOX-mTOR binding the pyrimidine synthesis from purines will activate by synthetase mitochondrial enzyme to contribute to the presence and availability of needed pyrimidine nucleotides for genes and protein synthesis including S6K1 genes and GTPase productions, where the tumor growth and contents can reflect the reductions in G-protein kinase and in PSTG Kinase pathways then consequently will reflect reductions in GTPase which will lead to increase in cells size and in its protein contents.

The Forkhead box O (FoxO) transcription factors are downstream targets of the serine/threonine-protein kinase B (PKB)/Akt, which regulates processes of cellular proliferation and survival **(**10**)**. And FOX genes are regulator genes for the four kinds of active protein kinases for running the protein and genes synthesis including the autophagy and tRNAs activation. The fact that the mTORC1 deregulation and reductions in autophagy are associated with several human diseases, such as type 2 diabetes, cancer, obesity, and neurodegenerative **(**11**)**.

FOXO3a activity is regulated by the activation of (nucleus and mitochondrial activities, where through the binding of mTOR to FOXO1 will produce mTORC1 complex and other "PIMs" proteins kinases. The stimulations and activations of FOX genes by chromosome and by mitochondria indicated that FOX genes have arranged gene sequences qualified for regulating all protein kinases productions and activities pathways including S6K1 and estrogen hormone synthesis pathways. The activated FOXO3a can induce autophagy effectors, gluconeogenic enzymes, and others **(**12**)** because mTORC1 which produced from the regulated PSTC kinase protein is having the same arranged regulated sequences from FOX genes and from the nucleus which is main for regulating autophagy activities and synthesis, sp any Disturbance or turbulence to those sequences will case effects in their produced products genes.

On the other hand, upon glucose restriction, 5′-AMP-activated protein kinase (AMPK) and mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) -dependent FOXO3 and mitochondrial translocation allows the transcription of oxidative phosphorylation (OXPHOS) genes, restoring cellular ATP levels **(**12**)**

Sestrin1, AMPK Autophagy, and more of activated proteins and genes by FOX genes which result from mTOR-FOX forkhead genes binding under modulations and regulations by phosphorylation Ser /Thr mechanism (PS/TM), mitochondrial enzymes effects, and ribosomes ATPase activities, are all mainly regulated by a nucleus, and regulated by ribosomal functions and activities depending on PS/TM, where the synthesized genes as S6K1 gene will derive to the inner chromosomes and ribosomal inner genes to ensure its genetic original compatibility with the ribosome and with chromosome and to restore the original compatibility if differences occurred in it as a result of inner cell metabolic processes.

The genes for the paired box proteins PAX3 and PAX7, respectively, can be fused to the FKHR (forkhead in rhabdomyosarcoma) gene on chromosome 13q14 **(**13**)**, where the chromosome 13q14 deletion syndrome is characterized by the retinoblastoma, variable degrees of mental impairment, and characteristic facial features, including high forehead, prominent philtrum, and anteverted earlobes, and indicate that the chromosome 13q14 gene is the main for ribosomal activities, for ROR alpha genes, and for FOX genes regulations and their produced genes and active proteins products and activities.

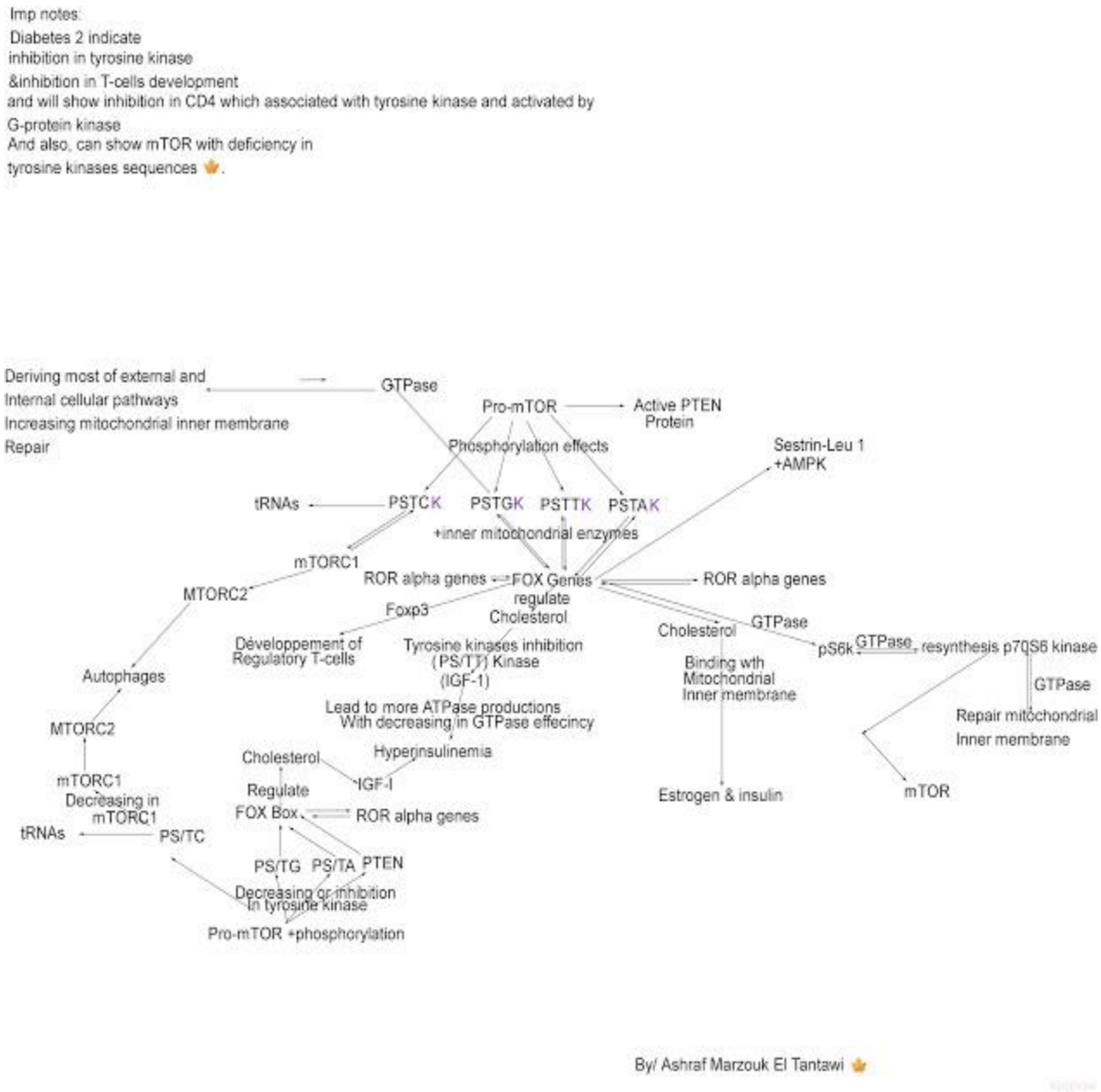
Imp notes:
Diabetes 2 indicate
inhibition in tyrosine kinase
&inhibition in T-cells development
and will show inhibition in CD4 which associated with tyrosine kinase and activated by
G-protein kinase
And also, can show mTOR with deficiency in
tyrosine kinases sequences
Deriving most of external and
Internal cellular pathways
Increasing mitochondrial inner membrane
Repair
GTPase
Pro-mTOR
Active PTEN
Protein
Phosphorylation effects
Sestrin-Leu 1
+AMPK
tRNAs
PSTCK
PSTGK
PSTTK
PSTAK
+inner mitochondrial enzymes
mTORC1
MTORC2
ROR alpha genes
FOX Genes
regulate
ROR alpha genes
Foxp3
Cholesterol
Développement of
Regulatory T-cells
Tyrosine kinases inhibition
(PS/TT) Kinase
(IGF-1)
Cholesterol
GTPase
pS6k
GTPase
resynthesis p70S6 kinase
Binding wth
Mitochondrial
Inner membrane
GTPase
Repair mitochondrial
Inner membrane
Autophages
MTORC2
Lead to more ATPase productions
With decreasing in GTPase effecincy
Hyperinsulinemia
Cholesterol
IGF-I
mTORC1
Decreasing in
mTORC1
Regulate
FOX Box
ROR alpha genes
tRNAs
PS/TC
PS/TG
PS/TA
PTEN
Decreasing or inhibition
In tyrosine kinase
Pro-mTOR +phosphorylation
Estrogen & insulin
mTOR
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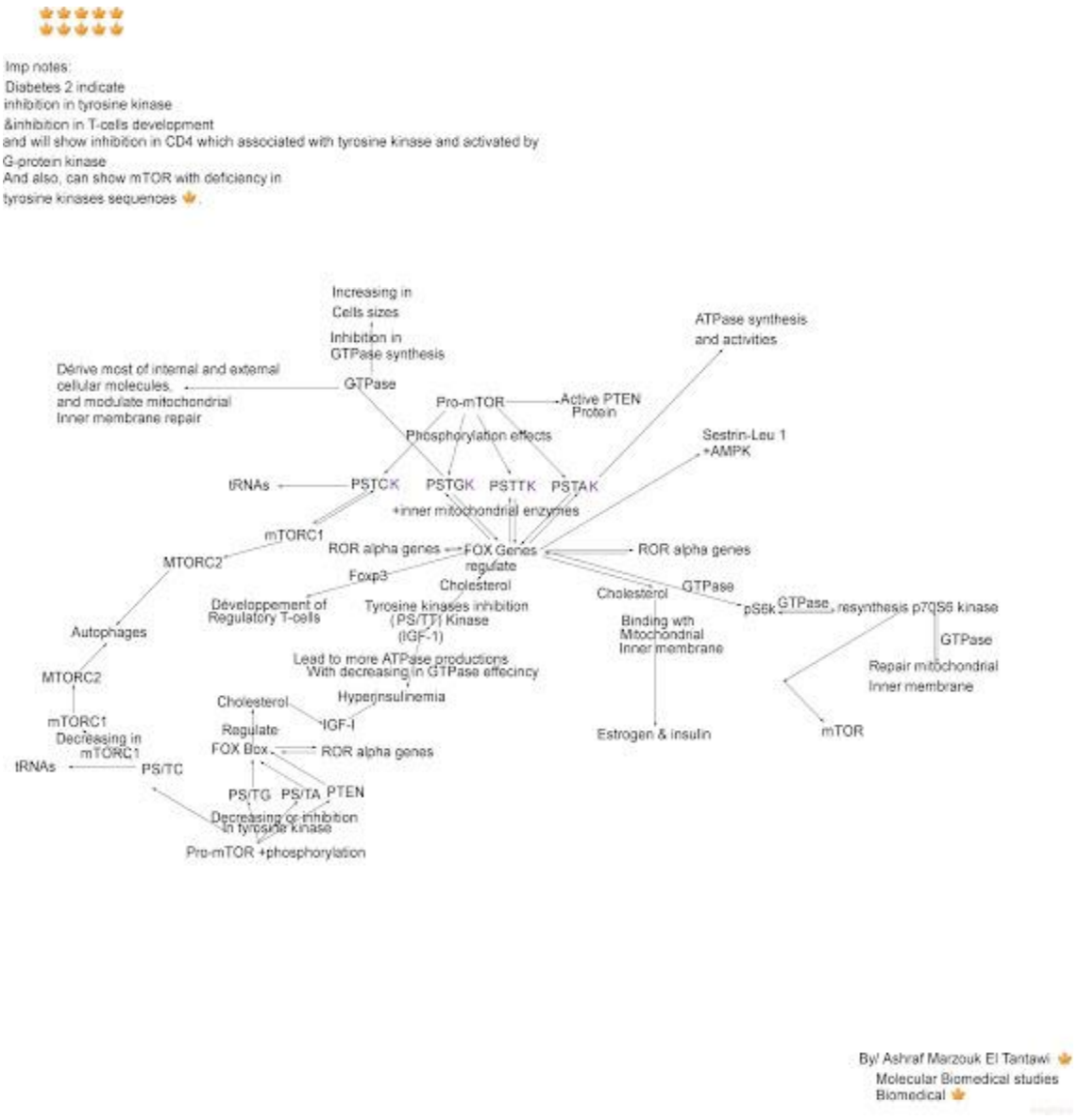
Figure 1


Imp notes:
Diabetes 2 indicate
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and will show inhibition in CD4 which associated with tyrosine kinase and activated by
G-protein kinase
And also, can show mTOR with deficiency in
tyrosine kinases sequences
Increasing in
Cells sizes
Inhibition in
GTPase synthesis
ATPase synthesis
and activities
Dérive most of internal and external
cellular molecules
and modulate mitochondrial
Inner membrane repair
GTPase
Pro-mTOR
Active PTEN
Protein
Phosphorylation effects
Sestrin-Leu 1
+AMPK
tRNAs
PSTCK
PSTGK
PSTTK
PSTAK
+inner mitochondrial enzymes
mTORC1
MTORC2
ROR alpha genes
FOX Genes
regulate
ROR alpha genes
Foxp3
Cholesterol
Développement of
Regulatory T-cells
Tyrosine kinases inhibition
(PS/TT) Kinase
(IGF-1)
Cholesterol
GTPase
pS6k
GTPase
resynthesis p70S6 kinase
Autophages
Binding wth
Mitochondrial
Inner membrane
GTPase
Repair mitochondrial
Inner membrane
Lead to more ATPase productions
With decreasing in GTPase effecincy
MTORC2
Cholesterol
Hyperinsulinemia
mTORC1
Decreasing in
mTORC1
Regulate
IGF-I
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Decreasing or inhibition
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Pro-mTOR +phosphorylation
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Molecular Biomedical studies
Biomedical

Figure 2

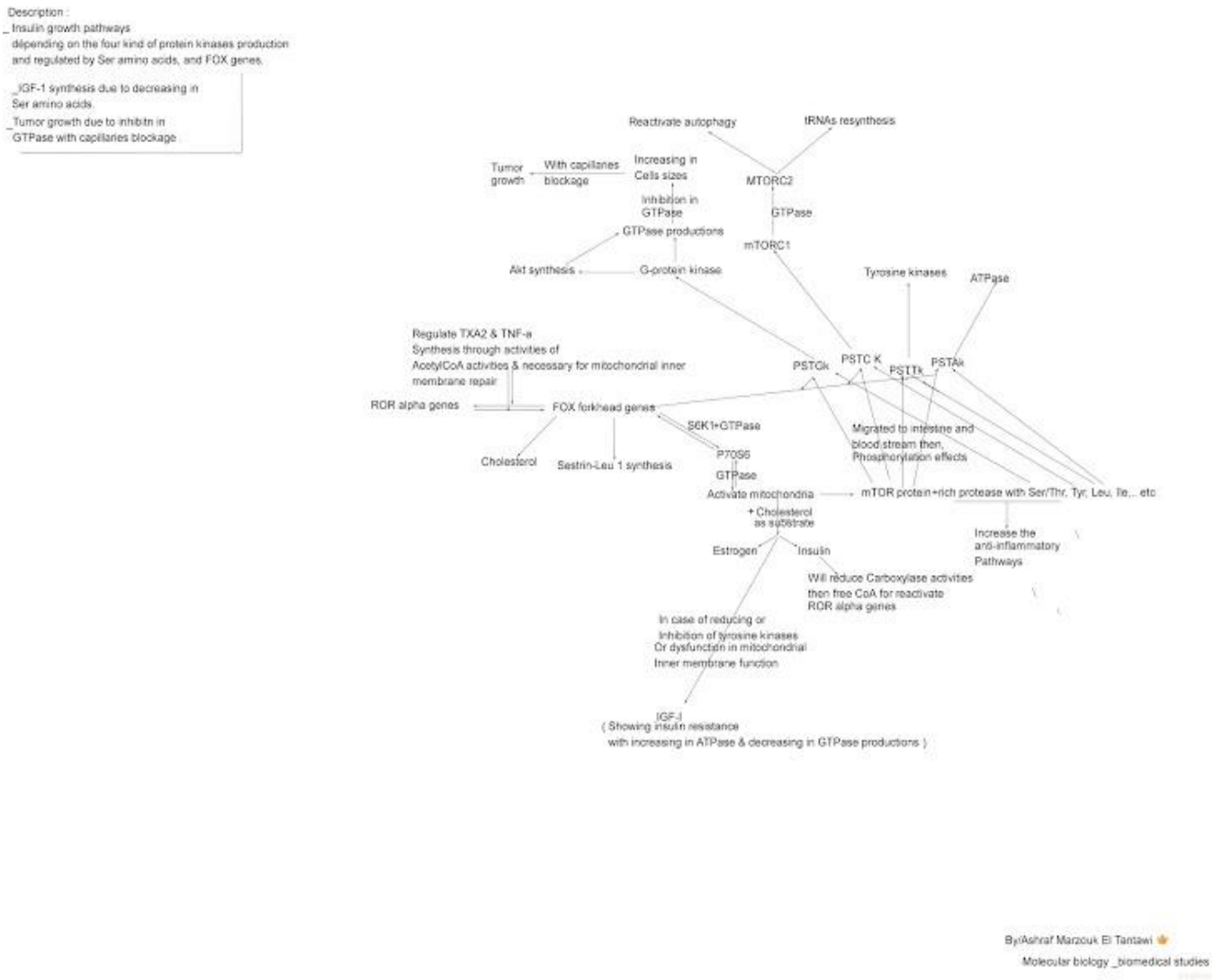

Figure 3

Methods:

The translational repressor, eukaryotic initiation factor 4E binding protein 1 (4E-BP1), and the 70-kDa ribosomal protein S6 kinase (S6K1) are important tools of protein and hormone synthesis pathways, and together they have and play regulations behavior of both eukaryotic initiation factors and ribosomal repairs and activities.

Both genes (4E-BP1) and S6K1 are so closely related to each other in functions and activities and are finally depending on the type and arrangement of nucleotides composition of sequences of S6K1 genes,

that when protein synthesis begins by phosphorylation step on initiation factor 4E-BP1 will be derived to S6K1 to insure the main original sequence in S6K1 that imp nucleotides will be saved and arranged in their proper sites and not necessary nucleotides will be discarded to be used in other cycles, then protein synthesis beginning.

MTOR genes are originated from ribosomal genes S6K1 and p70S6 with the mitochondrial regulations. The mTOR pathway is considered as a necessary tool for carrying necessary nutrients needs for regulating and activating necessary cellular pathways by which eukaryotic cells adjust the protein biosynthetic capacity, lipid metabolism, and hormone growth productions.

The regulation of activity of translational initiation factors activated and regulated by serine/threonine sites for phosphorylation mechanism, where, those two amino acids are the main to be involved in the mTOR genes and in the S6K1 gene which can be the repair stimulated gene sequence for p70S6 kinase.

The S6K1 which is the ribosomal main genes important for p70S6 repair and stimulated molecular structure, and is also for reinitiating mTOR genes synthesis carrying main necessary cells needs through specific nucleotides sequences for carrying specific protein sequences from nutrients for running necessary needed cellular metabolism eg for increasing anti-inflammatory tools as increasing TNF-a and TXA2 alpha subunits for VEGF-Alpha subunits synthesis for G-actin filaments activities and for tropomyosin isoforms reproduction the genetic deletion and pharmacological inhibition of The Ribosomal protein S6K1 is a downstream effector of mTORC1, blocked within-session extinction, indicating a role for S6K1 independent of protein synthesis **(**17**)** .

Stimulation and reactivating mTOR as well as its downstream substrates for stimulating and resynthesis (pS6k) ribosomal protein for p70S6 kinase repair and activities **(**18**)**.

The protein synthesis pathway is exquisitely sensitive to the availability of hormones, nutrients, and dépend on mTOR pathway activities started by phosphorylation and FOX genes binding steps for the four kinds of protein kinases production, for S6K1 production, and for cholesterol productions then estrogen and insulin synthesis pathways cycles.

The translational repressor, eukaryotic initiation factor 4E binding protein 1 (4E-BP1), and the 70-kDa ribosomal protein S6 kinase (S6K1) are important tools of protein and hormone synthesis pathways, and together they have and play regulations behavior of both eukaryotic initiation factors and ribosomal repairs and activities.

Both genes (4E-BP1) and S6K1 are so closely related to each other in functions and activities and are finally depending on the type and arrangement of nucleotides composition of sequences of S6K1 genes, that when protein synthesis begins by phosphorylation step on initiation factor 4E-BP1 will be derived to S6K1 to insure the main original sequence in S6K1 that imp nucleotides will be saved and arranged in their proper sites and not necessary nucleotides will be discarded to be used in other cycles, then protein synthesis beginning.

The reactivating pro-mTOR by phosphorylation and FOX genes binding pathways is the main source for reactivating the S6K1 genes consequently for 4E-BP1 synthesis in priority steps during the four kind of protein kinases synthesized due to phosphorylative steps, then 4E-BP1 will start the activities in controlled fine mechanisms with S6K1 genes functions for cells proliferation and protein synthesis metabolism.

In cases of dysfunction in mitochondrial inner membrane activities or dysfunction in tyrosine kinases proteins pathways synthesis, or with dysfunction in G-protein (Guanine kinase) PS/TG, both S6K1 and 4E-BP1 will have and show activities but with specific mutations due to their mutated composition in some kind of tumors in tissue cells, but their activities will reflect the accumulation of synthesized protein due deficiency in GTPase and due to missing in their necessary promoter in their protein chains that can reveal a deficiency in Thymine and Cytosine nucleotides that will not rebuild tyrosine or leucine or Ser/Thr amino acids. Also, the synthesis of S6K1 protein in some kind of tumors can be inhibited due to dysfunction in GTPase pathways production and due to decreasing in tyrosine and in Akt protein kinases synthesis where GTPase is necessarily produced from PSTG G-protein kinases with PSTT tyrosine kinases activities pathways and for the regulators of the actin-based cytoskeleton; that GTPases are key regulators of membranes traffic and Golgi transport. Consequently, the S6K1 synthesis will be inhibited when PSTG and or PSTT Kinases inhibited, but proliferation in some other tumors can be continued due to using the toxic Genes and proteases produced by bacteria and by viruses during the infection to living cells and living tissue.

The translational repressor eukaryotic initiation factor 4E-binding protein 1 (4E-BP1 is so necessary for mTORC1 synthesis and then for mTORC2 productions for tRNAs synthesis and for autophagy synthesis and activities.

TSC1 is produced due to phosphorylations effects on pro-mTOR too and is required to regulate and stabilize TSC2 (which is necessary for activating GTPase productions and activities) to prevent its ubiquitin-mediated proteasomal degradation. TSC1 is regulating TSC2 production and functions, where

TSC2 is a key player through GTPase activations in the regulation of the common mTOR pathway activities of protein synthesis, cell growth, and viability in response to cellular energy levels **(**19**)**.

The regulation of mTORC1 is achieved by mitogen, by the quality of nutrients, and by energy through phosphorylations processes on pro-mTOR. Where biguanides can inhibit mTORC1 signaling, not only in the absence of TSC1/2 but also in the absence of AMPK. the ability of biguanides to inhibit mTORC1 activation and signaling dependent on the Rag GTPases **(**20**)**.

That biguanide protein molecules can be considered as a partial step for reactivating G-protein kinase pathways and for reactivating GTPase synthesis than for FOX transcription genes activities and re-stabilities (with the availabilities of cytosine protein kinase PSTC, Tyrosine-protein kinase PSTT, and adenosine protein kinases PSTA) for running main necessary cellular metabolic pathways for Sestrins-Leu 1 synthesis, for S6K1 productions, for AMPK resynthesis, and for cholesterol synthesis through the FOX forkhead genes and ROR alpha genes regulations for mitochondrial binding than for insulin growth synthesis.

The translational repressor eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) is stimulated through phosphorylation effects on pro-mTOR at multiple sites for producing mTORC1 complex too, which has a function and activities for tRNAs productions and for autophagy productions, and is strongly linked with S6K1 synthesis and activities.

That 4E-BP1 contains two regulatory motifs: the C-terminal TOS motif interacts with the mTOR-binding partner, raptor, and mediates phosphorylation of specific sites in 4E-BP1.**(**21**)**.

Activated FOXO-mediated insulin resistance can be blocked through the reduction in TOR activity.

In spite of the FOXO1 is regulating cholesterol which is the insulin substrate, the FOX genes are still need feeding and the supports from mTOR active protein through the supplements of G-protein (Akt), PSTT, and PSTA where, PSTA and PSTG (Akt) which are so necessary for ATPase and GTPase re-activities, where the tyrosine Kinase (PSTT) is so necessary for Sestrins-Leu 1 synthesis and are necessary for increasing the FOX gene stabilities which needed for regulating and modifying cholesterol in a proper molecular composition structure for the re-stimulate the insulin synthesis.

Where The presence of hydrophobic amino acids as Tyr, Leu, and presence of Ser, and Thr amino acids in tyrosine kinase, and in G-protein kinases molecular synthesis, with a lower limit of adenosine kinase protein contributions through FOX forkhead genes binding are so necessary for proper cholesterol synthesis and for insulin growth and any improvement in the increasing of those active amino acids will

be done by mitochondrial synthetase enzyme that will convert extra purines to active pyrimidine nucleotides for synthesis the mission of those amino acids.

The acetyl-CoA synthase which is formed for mitochondrial inner membrane binding with cholesterol for insulin hormone production with S6K1 and p70S6 regulations with original regulation by ROR alpha genes and by FOX transcription forkhead genes, and so necessary for insulin synthesis with GTPase regulations.

The pS6k can be considered as it can be stimulated and regulated directly from mTOR by phosphorylation effects for stimulating and reactivate p70S6

The Phosphorylation effects on pro-mTOR will produce four kinds of proteins: PSTT, PSTG, PSTA and PSTC active proteins with PTEN production during the binding with FOX forkhead genes, that can be the main reason for increasing the stabilities and activities of FOX forkhead genes, and will lead to PS6K genes productions that will be derived directly for refeeding the p70S6 ribosome for its stabilities and reactivities in cells for mitochondrial inner membrane repairs and activations, and for antigens resynthesis, where the previous antigen resynthesis will need the contributions of the four kind protein kinases specifically the G-protein kinase PSTG, PSTT, PSTA Kinases, the PTEN productions, and S6K1 genes for re-activating its original sequences with the regulation of ribosomal p70S6 and GTPase productions.

In case of decreasing in GTPase with increasing in ATPase means decreasing in G-protein kinase and increasing in adenosine kinase protein which will lead to increase in catalyzing and in digesting adenosine protein kinase that will lead to increasing in cells size and decreasing in migrating the new produced inner biological molecules, where deriving the filtered nutrients protein kinase molecules (which produced due to phosphorylation on pro-mTOR during FOX binding) to inner cells due to reduction or inhibition in GTPase which will lead molecules to abide, remains, and stay within inner cells without migration, that can reflect the reduction in G-protein kinase productions due to phosphorylations effects.

The Rho GTPases are key regulators of actin-based cytoskeleton, and Rab GTPases are the key regulators of membrane traffic, and also, Rho GTPase required for endosome to Golgi transport **(**22**)**. That the deficiency in G-protein kinase will reflect a deficiency in GTPase synthesis and will lead to staying and remaining of new protein and genes derived from mTOR bonded with FOX genes inside cells.

Also, mutations in dS6K protein affect only cell size but not cell number, indicating that dS6K is a distal effector in the signaling pathway, directly controlled by dTOR **(**23**)**, which indicate that PS6K is mainly

formed from G-protein (PSTG) and tyrosine (PSTT) kinases and depending on the GTPase regulations, and are derived to the cells with some problems kinases (PSTG, PSTT, & PSTA)for antigen repairs and then for ribosomal p70S6 stimulations and reactivation.

The increase in phosphorylations effects on proper healthy pro-mTOR protein will increase the phosphatase and tensin homolog PTEN that act as active enzymes that can lead to converting the folded genes proteins into unfolded active proteins, depending on the amount of the bonding energy involved in folded protein and on amount of produced energy.

Productions of PTEN protein will be used in metabolizing the Akt, hydrophobic amino acids, S6K1 genes, cholesterol, and then estrogen and insulin production, and also for GTPase synthesis in extracellular interstitium fluid and within living cells.

Insulin resistance and the compensatory hyperinsulinemia provoke increased androgen synthesis with high ATPase activities at the expense of decreasing estrogen production. The decrease in estrogen reflect decreasing in PSTG and PSTT Kinase protein and consequently reflect decreasing in GTPase synthesis and activities that will lead to using PSTA protein Kinase by inner cells instead of other missed kinases for cellular metabolic cycles, which will lead to Increasing in adenosine metabolism but specificity catabolic cycles that will lead to increase in ATPase productions and activities with a reduction in GTPase productions and activities, which will lead to a deficiency in lipid metabolism with increasing in carbohydrate metabolism by ATPase activities, with decreasing in the control of hormone synthesis and balance, that will lead increasing in blood sugar, and cholesterol, with increasing in the mutated insulin-like IGF-I molecules which will reflect the lacking guanine and Thymine nucleotides which reflect lacking in tyrosine, Leu, Ser, and Thr amino acids.

In other hands, normal estrogen normal can be synthesised through phosphorylation effects mechanism on pro-mTOR protein through using both Therionine and serine amino acids for degrade the Pro-mTOR for the four kind of protein kinases productions depends on nutrients quality and quantity of necessary amino acids content including serine and Threonine, that at deficiency in Ser amino acid and with increasing in Thr will lead to increasing in insulin levels (but does not contains normal sequences) and that accompanied with increasing in ATPase synthesis and with decreasing in GTPase and Thymine nucleotides (pyrimidine) which involved in Ser triplet amino acid , that Thymine is the main for Tyrosine kinases Proteins productions from pro-mTOR protein, also is main for S6K1 gene synthesis , and main for mTORC1 synthesis (which considered to be the main regulator for mTORC2 for tRNAs and for autophagy synthesis and reactivities , and also involved in S6K1& ribosome p70S6 genes repairs and

re-activities which need to be repair due to cells metabolic cycles including their activities in energy protection and normal oxidations processes).

So in deeply brief, the hyperinsulinemia begin with the deficiency in Ser amino acids which supposed to be involved in Pro-mTOR protein or resynthesized during FOX genes binding by the contributions and regulations by mitochondrial synthetase enzymes, and consequently, hyperinsulinemia will reflect decreasing in Thymine nucleotides which supposed to be included in Serin amino acid, that will reflect and will lead to decreasing in Tyrosine (TAT TAC) kinases proteins production, in Leu amino acids synthesis, and also referred decreasing in mTORC1 productions too.

The altered tyrosine kinase activity of the insulin receptor is an important factor in diabetic animal models of insulin resistance also, a decrease in the maximum response to insulin, the responsible alteration is more likely to involve post kinase processes **(**24**)**. That support by re-increasing Thymine in the blood may be temporary key if patients have broken mitochondrial inner membrane and have broken ribosome, so the support may include S6K1 genes and the ensure of the availabilities of converting folded proteins to active unfolded protein during some necessary cellular metabolic cycles as estrogen re synthesis whether from regulated cholesterol from FOX and ROR alpha genes or carefully from androgen through increasing GTPase regulation more than ATPase in specified limits for understanding the regulated controls for specific cycles.

The insulin resistance may be under tonic inhibition by serine phosphorylation and that the factors responsible for this may be upregulated during pregnancy **(**25**)**, where, if phosphorylation occurs using Serine (TCG, TCA, or TCT) mechanism will release Thymine which is so necessary for tyrosine synthesis with support from mitochondrial synthetase enzyme for converting and adjust the more converted purines to pyrimidine for leucine, for tyrosine and for other hydrophobic amino acids synthesis which are necessary and needed for estrogen and insulin synthesis.

The stimulatory factor-1, insulin, insulin-like growth factor-1 (IGF-1) productions are fully dependent on PPARs genes, epidermal growth factor (EGF), hepatocyte growth factor (HGF), and platelet-derived growth factor (PDGF)**)**, where PPARs genes fully depend on the threonine active phosphorylation mechanism activities, indicating IGF-1 activity is also depending on threonine phosphorylation mechanism only, so a deficiency of Ser amino acids the cells will be forced and their cycles to depend only on threonine amino for hormones and insulin synthesis, where only threonine mechanism will not produce normal insulin with normal sequences but will produce IGF-I which will depend only on threonine phosphorylations mechanism (ACC, ACA, or ACG)

activities (due to a deficiency in Ser phosphorylation mechanism) , that will lead to release the only Cytosine and adenine nucleotides which will lead to product and synthesis of only adenosine protein kinase protein and the other two kinases protein (PSTCk +PSTCk) but with a full deficiency in Thymine nucleotides and consequently deficiency in Thymine protein kinase ((which is the tyrosine-protein kinase). So a deficiency in Ser nucleotides will lead to Increasing in ATPase productions and in their activities, which will reflect the decrease in tyrosine kinases protein (Thymine protein kinase) production that reflect deficiency in hydrophobic amino acids synthesis which originally depending on Thymine (pyrimidine)nucleotides which is the basis in Serine triplet amino acids and is the basis in Ser phosphorylation mechanism, that have to be included in Pro-mTOR proteins and have to be recovered by synthetase mitochondrial enzymes activities.

The deficiency in Thymine nucleotides and their in tyrosine-protein kinase (Thymine protein kinase "PSTTk") in the estrogen hormone synthesis and in its metabolic pathways is the result of IGF-I synthesis which lead to insulin resistance and positively can increase the risk of cancers and other diseases as cardiovascular disease, particularly in the organs having high estrogen demand (breast).

The mutations that occurred due to deficiency in Ser amino acids will lead to consequently mutated S6K1 ribosome p70S6, deficiency in sestrin-Leu-1 synthesis, decreasing in FOX forkhead genes stabilities, and lead to mutations in mitochondrial inner membrane LOPA1 gene.

The deficiency in Ser amino acids will reflect a deficiency in pyrimidine Thymine nucleotides in the pro-mTOR metabolic pathways, which will lead to IGF-I production instead of normal insulin production in vivo…

Bile salts, the major constituent of bile, solubilize dietary lipids, that bile has main function and contribution for solubilities of dietary lipid to be involved in Pro-mTOR protein for easier full digestion for G-protein kinase synthesis from phosphorylation on mTOR protein binds with FOX forkhead genes than for PSTG Kinase productions by phosphorylation for Akt production and for cholesterol productions which will be the insulin and estrogen substrate by the regulation of S6K1 and p70S6 ribosomal genes and mitochondrial membrane for later protein synthesis and mTOR resynthesis for again recycling the dietary digestive components.

The StAR protein synthesis is translocated with a typical mitochondrial membrane and depending on the G-protein kinase PSTG, Cytosine protein kinase PSTC, and on tyrosine-protein PSTT kinases which necessary for hormones synthesis by S6K1 produced genes with GTPase and mitochondria regulation for active hormones synthesis which will need the binding with Luteinizing hormone produced by gonadotropic cells.

hydroxymethylglutaryl-CoA (HMG-CoA) reductase molecules is depending on the availabilities of guanine nucleotides activity which is necessary for reactivating directly Leu (CTG, TTG) and GTPase regulations indirectly notice Gln amino acids is necessary for Leucine production by Gln amino acids (CAG, AAC), also, guanine is necessary for Tyr (TAG) amino acids which is so necessary for brain reactivities specifically for Enkephalin pentapeptides functions, and for Sestrins-Leu-1 synthesis through phosphorylation on FOX-mTOR binding and mitochondrial regulations in the cellular metabolic pathways.

FOXP3 is a member of the FOX protein family, appears as a master regulator of the development and functions of regulatory T cells.

The expression of the FOX forkhead transcription factor to protein P3 (FOXP3) is characteristic of Treg cells, and is centrally involved in the establishment and maintenance of the Treg cell.

The lymphocyte-specific protein tyrosine kinase LCK phosphorylates FOXP3 in cancer cells at Y342 **(**26**)**.

The availabilities of Ser amino acids in FOXP3 genes are so necessary for its functions and for all linked anabolic cycles, where Phosphorylation at Ser-418 regulates its transcriptional FOX activity and consequently, regulatory T-cells (Treg) suppressive function. But Phosphorylation by CDK2 (which depend on Thr phosphorylation mechanism)

will not activate FOX forkhead gene functions, which indicate that the presence of Thymine in Ser triplet is the main active nucleotides for FOX genes, for tyrosine, and for Cytosine kinases production. Where the four kinds of protein kinases produced from pro-mTOR protein are necessary for regulating T-cells synthesis specifically Cytosine kinases protein (PSTC Kinase) for mTORC1 synthesis which regulates mTORC2 and then regarded autophagy.

Tyrosine-protein kinase is a regulator to promote Treg cell production where JAKs which are kinds of tyrosine kinases are bound to the cytoplasmic, that STAT5 binds to the promoter of the FoxP3 gene and it can promote Treg cells **(**27**)**.

CDK5, Cyclin-dependent kinase 5, Activated by retinoic acid **(**28**)**, indicating that CDK5 is regulated also by ROR-alpha genes.

Results and conclusions:

Pro-mTOR protein is the stimulated mTOR by the ribosome and inner mitochondrial activity that bind to absorbed nutrients molecules which includes proteins, lipid and carbohydrate, that will be derived to be phosphorylated during the binding with FOX forkhead genes where phosphorylations are so necessary to be It is well illustrated and described as it is the basis of the pro-mTOR metabolic cycles, that any deficiency in the Serine triplet or Serine itself will lead to differences and mutations in most of metabolic cycles products, where that phosphorylation is only can be done by Ser/Thr phosphorylation mechanism that will produce four kinds of protein kinases according to the four free nucleotides which released from Ser /Thr ph. The mechanism, which is: PSTCk, PSTGk, PSTTk, and PSTAk. Those protein kinases each will follow their own necessary pathways and in the same time is Contributing and modulating other kinases pathways.

Normal cholesterol molecules are normally originated from Ser/Thr phosphorylation mechanism that will be derived to the inner mitochondrial membrane to be regulated and modified to be a proper substrate for stimulating insulin growth, but at deficiency in Ser amino acids will reflect a deficiency in Thymine nucleotides and its protein kinase (PSTTk) productions that will lead to force cellular pathways to use only Thr phosphorylation mechanism that will produce only adenosine protein kinase and decreasing in Guanine protein kinase "the G-protein kinase" with Cytosine protein kinase (PSTCk) that results will lead to IGF-I synthesis and production which lack the Thymine nucleotides in its molecular structure, that will lead diabetes 2 to and later can lead to cancer.

Deficiency in Ser amino acids also will lead to mutated S6K1 gene protein lead to mutations or dysfunction in ribosomal p70S6 genes activities.

Decreasing or deficiency in Guanine protein kinase (G-protein kinase) productions from pro-mTOR binding with FOX forkhead genes mechanism will lead to decreasing or inhibition in GTPase synthesis and activities, lead to increase in cells size that leads to capillaries blockage and tumor growth.

The deficiency in Cytosine protein kinases (PSTCk) leads to decreasing in mTORC1 productions with decreasing in tRNAs productions (lead to tumor growth) and leads to decreasing in mTORC2 production and in autophagy synthesis and activities.

Also, the reduction in adenosine protein kinase leads to severe reductions in ATPase productions and activities lead to decreasing in blood pressure and failure in heart functions.

ESTROGEN (EPK) is hormone synthesis from PSTT with PSTG protein kinases which are formed mainly from Ser phosphorylation mechanism on pro-mTOR during binding with FOX forkhead genes,

But androgen (APK) is a hormone formed from PSTA with PSTC protein kinases and depends on threonine phosphorylation mechanism effects on pro-mTOR protein during the binding with FOX forkhead genes. Where estrogen has strong stimulated pathways activities with brain, heart, and all of the upper living cells and its regulation has strong linkages with GTPase synthesis and activities, consequently EPK has strong connections with anabolic processes and protein synthesis.

But androgen has strong linkages with ATPase synthesis and activities consequently has strong linkages with catabolic processes.

Conflict of Interest Statement:

The authors declare that the research work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1.“Regulation of mTORC1 and its impact on gene expression at a glance” Mathieu Laplante and David M. SabatiniCell Sci. 2013 Apr 15; 126(8): 1713–1719. doi: 10.1242/jcs.125773 PMCID: PMC3678406 PMID: 23641065

2.“The mTOR Pathway in the Control of Protein Synthesis” Xuemin Wang, and Christopher G. Proud Published Online:01 OCT 2006 https://doi.org/10.1152/physiol.00024.2006.

3.Laplante M, Sabatini DM (April 2012). "mTOR signaling in growth control and disease". Cell. 149 (2): 274–93. doi:10.1016/j.cell.2012.03.017. PMC 3331679. PMID 22500797.

4.Chen X, Liu M, Tian Y, Li J, Qi Y, Zhao D, et al. (May 2018). "Cryo-EM structure of human mTOR complex 2". Cell Research. 28 (5): 518–528. doi:10.1038/s41422-018-0029-3. PMC 5951902. PMID 29567957.

5.“Targeting autophagy-related protein kinases for potential therapeutic purpose” Author links open overlay panel Honggang Xianga† Liang Ouyangac https://doi.org/10.1016/j.apsb.2019.10.003 Get rights and content

6. “Mitochondrial GTP Links Nutrient Sensing to β Cell Health, Mitochondrial Morphology, and Insulin Secretion Independent of OxPhos” Author links open overlay panelSean R.Jesinkey18Richard G.Kibbey129 https://doi.org/10.1016/j.celrep.2019.06.058 Get rights and content Under a Creative.

7. “A systems study reveals concurrent activation of AMPK and mTOR by amino acids” Piero Dalle Pezze, Stefanie Ruf, […]Kathrin Thedieck Nature Communications volume 7, Article number: 13254. Published 21 November 2016. DOI https://doi.org/10.1038/ncomms13254

8. “A novel classification of colorectal tumors based on microsatellite instability, the CpG island methylator phenotype and chromosomal instability: implications for prognosis” C.C.J.M. Simons L.A.E. Hughes K.M. Smits P.A. van den Brandt M.P. Weijenberg † M. van Engeland † Show all authors DOI:https://doi.org/10.1093/annonc/mdt076.

9. “The mTOR Pathway in the Control of Protein Synthesis” Xuemin Wang, and Christopher G. Proud Published Online:01 OCT 2006 https://doi.org/10.1152/physiol.00024.2006.

10. “Akt, FoxO and regulation of apoptosis” Author links open overlay panelXinboZhangbdArun K.Rishiabc https://doi.org/10.1016/j.bbamcr.2011.03.010.

11. “Regulation of mTORC1 and its impact on gene expression at a glance” Mathieu Laplante and David M. Sabatini. 2013 Apr 15; 126(8): 1713–1719. doi: 10.1242/jcs.125773 PMCID: PMC3678406. PMID: 23641065.

12. “FOXO3a from the Nucleus to the Mitochondria: A Round Trip in Cellular Stress Response” Candida Fasano, Vittoria Disciglio, […], and Cristiano Simone Published online 2019 Sep 19. doi: 10.3390/cells8091110 PMCID: PMC6769815 PMID: 31546924

13. “Cloning and Characterization of Three Human Forkhead Genes That Comprise an FKHR-like Gene Subfamily” Author links open overlay panelMichael J.AndersonaKaren C.Ardenab https://doi.org/10.1006/geno.1997.5122.

14. “The Emerging Roles of mTORC1 in Macromanaging Autophagy” Akpedje S. Dossou and Alakananda Basu. Published online 2019 Sep 24. doi: 10.3390/cancers11101422PMCID: PMC6826502 PMID: 31554253.

15. Serova LI, Filipenko M, Schilt N, Veerasirikul M, Sabban EL. “Estrogen-triggered activation of GTP cyclohydrolase 1 gene expression: role of estrogen receptor subtypes and interaction with cyclic AMP”. Neuroscience. 2006 Jul 21;140(4):1253-63. doi: 10.1016/j.neuroscience.2006.03.017. Epub 2006 May 2. PMID: 16650618.

16. “Serine-threonine protein phosphatases: Lost in translation″ Cite

https://doi.org/10.1016/j.bbamcr.2018.08.006Get rights and content

17. Huynh TN, Santini E, Mojica E, Fink AE, Hall BS, Fetcho RN, Grosenick L, Deisseroth K, LeDoux JE, Liston C, Klann E. “Activation of a novel p70 S6 kinase 1-dependent intracellular cascade in the basolateral nucleus of the amygdala is required for the acquisition of extinction memory”. Mol Psychiatry. 2018 Jun;23(6):1394-1401. doi: 10.1038/mp.2017.99. Epub 2017 May 2. PMID: 28461701; PMCID: PMC5668214..

18. “Cryptotanshinone activates AMPK-TSC2 axis leading to inhibition of mTORC1 signaling in cancer cells” January 2017BMC Cancer 17(1) DOI: 10.1186/s12885-016-3038-y.

19.“TSC2 Mediates Cellular Energy Response to Control Cell Growth and Survival” Author links open overlay panelKenInoki12Kun-LiangGuan123 https://doi.org/10.1016/S0092-8674(03)00929-2

20. “Metformin, Independent of AMPK, Inhibits mTORC1 in a Rag GTPase-Dependent Manner” Author links open overlay panel Adem Kalender 1211 George Thomas 12

https://doi.org/10.1016/j.cmet.2010.03.014.

21 “Proud CG. mTOR-mediated regulation of translation factors by amino acids”. Biochem Biophys Res Commun. 2004 Jan 9;313(2):429-36. doi: 10.1016/j.bbrc.2003.07.015. PMID: 14684180.

22.Published in final edited form as: Cell. 2009 May 29; 137(5): 938–948. doi: 10.1016/j.cell.2009.03.043 PMCID: PMC2801561 NIHMSID: NIHMS108740 PMID: 19490898.

23. Radimerski T, Montagne J, Rintelen F, Stocker H, van der Kaay J, Downes CP, Hafen E, Thomas G. "dS6K-regulated cell growth is dPKB/dPI(3)K-independent, but requires dPDK1". Nat Cell Biol. 2002 Mar;4(3):251-5. doi: 10.1038/ncb763. PMID: 11862217.

24. Vol. 261, No. 1, Issue of January 5, ~p: 147-153,1986 nnted m U.S.A. "Alterations in the Tyrosine Kinase Activity of the Insulin Receptor Produced by in Vitro Hyperinsulinemia", (Received for publication, June 10,1985) Greg ArsenisS and James N. Livingston From the Department of Medicine, The University of Rochester, School of Medicine and Dentistry, Rochester, New York 14642.

25. "Decreased Insulin Receptor Tyrosine Kinase Activity and Plasma Cell Membrane Glycoprotein-1 Overexpression in Skeletal Muscle From Obese Women With Gestational Diabetes Mellitus (GDM) Evidence for Increased Serine/Threonine Phosphorylation in Pregnancy and GDM" Jianhua Shao, Patrick M. Catalano, Hiroshi Yamashita, Irene Ruyter, Steven Smith, Jack Youngren, and Jacob E. Friedman. DIABETES, VOL. 49, APRIL 2000.

26. "The regulation of immune tolerance by FOXP3" Ling Lu, Joseph Barbi, and Fan Pan.. Nat Rev Immunol. 2017 Nov; 17(11): 703–717. Published online 2017 Jul 31. doi: 10.1038/nri.2017.75 PMCID: PMC5793224 NIHMSID: NIHMS936105 PMID: 28757603

27. Seif, F., Khoshmirsafa, M., Aazami, H. et al. "The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells". Cell Commun Signal 15, 23 (2017). https://doi.org/10.1186/s12964-017-0177-y.

28. "The Fox and the Rabbits—Environmental Variables and Population Genetics (1) Replication Problems in Association Studies and the Untapped Power of GWAS (2) Vitamin A Deficiency, Herpes Simplex Reactivation and Other Causes of Alzheimer's Disease". C. J. Carter1 Academic Editor: A. Conti Volume 2011 |Article ID 394678 | https://doi.org/10.5402/2011/394678. Published12 Jul 2011

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