An in-depth study of TCA cycles, OPA1, S6K1, ATPase, TLR4, MHC-class-I, GCs, and IFNs bio-synthesis, and their roles of deficiency in diabetes, asthma, cancer etc., and the NAD roles in their activities

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The Purpose of this study

The roles of S6K1 in ATPase, in GTPase synthesis, and consequently in proliferation including endocytic soluble MHC class II synthesis and functions, that diabetes reflect deficiency in pyrimidines synthesis consequently deficiency in estrogen and reflect androgen synthesis with increasing in consuming in purines (A&G) that lead to decreasing in anabolic processes and proliferations.
OPA1-synthetase enzymes are so important for producing amino-acyl-CoA-synthetase (gamma-subunits) which considered as basics for regulating glucocorticoids synthesis, Interferon’s isoforms productions, for reactivating macrophages, for MHC class-I synthesis then consequently for endocytic soluble MHC class II synthesis and their endocytic root functions, and then for cellular proliferation.

S6K1 consider as protected basic subunits for Interferons (IFNs) isoforms synthesis regulated by pyrimidine-kinases. Asthma is characterized by Prediabetes and diabetes, that reasons of the occurrence the two diseases (Asthma & diabetes) are same. Estrogen formed from Ser/Thr mTOR FOX signaling pathways for glucocorticoids synthesis Upon OPA1 enzymes effects on estrogen, but the feedback of GC to produce estrogen will be upon ATPase on GCs isoforms.

Abstract

The purines and pyrimidines synthesis in vivo are the main basic processes for all of proper active subunits and active genes biosynthesis and for all cellular biological processes where any delays in their production or deficiency in some of their purines or pyrimidine will lead to symptoms of diseases, whether dangerous or benign.

Mitochondrial TCA cycles are a regulated metabolite related and depending on FOX genes functions and on ATPase with cox activities on carbohydrate, on lipid, and on proteins pro-nutrients-mTOR molecules for producing first long fatty acids chains and lipo-polysaccharides (LPS molecules ) , where, as FOX genes produce the four gps of kinases ( PSTCK, PSTTK, PSTGk and PSTA-kinases), as the mitochondrial enzymes (synthetase, synthase and phospholipase) will start their oxidative processes for modifying those four kinases gps for producing only three fatty acyl-CoA isoforms.

The full releasing of PSTGk and PSTAk gps depending on FOX functions and on ATPase with COX enzymes for S6K1 peptides synthesis (which are full of purines mainly adenosine nucleotides for ATPase repair ) which will be directed to ribosome granules within cells for further modification efforts by OPA1 enzymes for firstly pyrimidine synthesis then producing gamma-subunits upon Gamma-oxidations by synthetase enzymes , where, I consider that the releasing of PSTGk and PSTAk are the TCA cycles
for producing purines kinases or acyl-CoA-purines, (after mitochondrial OPA1 modification effects), where TCA processed normally related and concluded in the releasing of PSTT-Kinase and PSTC-kinase chains (mTORC1) which are depending on synthetase enzymes for pyrimidines synthesis. S6K1 synthesis and functions can controls tubulin acetylation (due to S6K1 is main regulator active peptides for ribosomal repairs and ATPase productions), hence S6K1 active subunits are contributing to the autophagic flux induced by different stress conditions and in different cells.

mTORC1 is the substrates (the basis for regulating S6K1 peptides productions) of regulating and stimulating ribosomal S6-protein-kinase-1 (S6K1) synthesis through Fox Serine/Threonine signalling activated pathways in response to nutrients and growth factors.

The availabilities of proline (Pro), Arg, Ser, Thr, Leu, and Tyr amino acids in S6K proper peptides will enhance the proper functions of ATPase and its productions which can prevent cancer, coagulation, prevent platelets aggregation, prevent bones weaknesses and erosion of the vertebrae, and prevent diseases symptoms. Na+, K+-ATPase membrane bonding enzymes (MBE) adopt hypertension, where, The NA+, K+_ATPase (MBE) functions is stabilizing cellls membranes signals activities and adopt the - ve charges signals transmission that adopt and stabilizing brain activities.

Estrogen formed from Ser/Thr mTOR Fox signaling pathways for glucocorticoids synthesis (the substrat of GCs synthesis) Upon OPA1 enzymes effects on Estrogen, but the feedback of GCs to produce estrogen will upon ATPase & COX regulations on GCs isoforms.

S6K1 consider as protected basic subunits for Interferons (IFNs) isoforms synthesis regulated by pyrimidine-kinases. Asthma is characterized by Prediabetes and diabetes, that reasons of occurrence the two diseases are same.

Where, positively Asthma is characterized by diabetes symptoms May in the early days of asthma cannot detected but after early days of diabetes can be detected.

MHC Class-I is fatty-acyl-CoA gamma-subunits (IFN-gamma) for modifying their fatty acyl-CoA-beta (IFN-beta) synthesis to be sit and lie on nucleated cells as MHC class-1 for endocytic MHC class-II production which will promote SIRPa synthesis for TLR4 productions.
Signal regulatory protein α SIRP (SIRP-α) is the basis for producing IFN-beta then IFN-alpha which activate TLR4 for Plasma membrane synthesis where through feedback will produce firstly MHC class II (IFN-beta upon synthase beta-oxidation) followed by gamma-oxidation for producing MHC Class-I. SIRP-gamma (IFN-gamma) productions from myeloid are necessary for acting fast on inflammations and infection-ed cells for analyzing their contents then bind to resulted peptides for modifying its own sensor subunits for promoting the productions of MHC class-I and SIRP-2-Beta (IFN-beta) upon regulations effects of OPA1 synthase enzyme which will directed to nucleated cells membranes to sit and lie on as MHC class-I which will promote the the endocytic soluble MHC class II.

The role of functions of the OPA1 oxidations cycles in producing S6K1 for ATPase for producing and for functioning the fatty-acyl-CoAs for producing NADH and then ATPase.

Decreasing or deficiency in S6K1 production will reflect the decreasing in the ATPase which also reflect the decreasing in mitochondrial OPA1-oxidations and decreasing in NAD and FAD that reflect the beginning of many diseases as asthma, diabetes, cancers... etc.

**Keywords:**

-TCA cycles functions

-S6K1 for ATPase synthesis

-IFN-isoforms

-TLR4

-MHC-class-I

-MHC-class-II

-Four kinds of proteins kinases groups

-SIRP-gamma, SIRP-beta & SIRPa

-T-cells

-B-cells
Materials:

- FOX genes,
- S6K1, ATPase and GTPase
- OPA1 enzymes,
- MTORC1, PS/T-Thymine-K, PS/T-Adenosene-k, PS/T-Guanosine-kinases
- Fatty-acyl-CoA-synthetase,
- Fatty-acyl-CoA-synthase,
- Fatty-acyl-CoA-phospholipase
- N’A, K, ATPase
- Renal proximal tubule epithelia,
- Beta-cells and beta chains
- CD8 T cells
- IFN-gamma, IFN-beta, and IFN-alpha
- diabetes and asthma studies
- MHC Class-I, MHC class II
- Signal proteins
- Tyrosine metabolic pathways
- Arg metabolism and proline synthesis
- mast cells
- Nicotinamide adenine dinucleotide, oxidized form (NAD+).
- T-cells
- B-cells
- TGF-gamma, beta, alpha
- TLR4
- myeloid cells
Methods are results

TCA cycles improves antibody, cytokines and acetyl-CoA production [1].

Mitochondrial TCA cycles are a regulated metabolite, which considered as a part from FOX genes activities and depending on FOX functions, on ATPase, and on OPA1 enzymes activities on carbohydrate, on lipid, and on proteins nutrient molecules., where, as FOX genes produce the four gps of kinases (PSTck, PSTTK, PSTGk and PSTA-kinases) as mitochondrial enzymes will start their oxidative effect for modifying those four kinases gps for producing only three fatty acyl-CoA isoforms.

The full releasing of PSTGk and PSTAk gps depending on FOX functions and on ATPase with COX enzymes I considered them as TCA cycles for producing purines kinases or acyl-CoA-purines, which normaly concluded the release of PSTT-Kinase and PSTC-kinase (mTORC1) which are depending on synthetase enzymes for pyrimidines synthesis (cytosine and Thymines) for hydrophobic amino acids [2].

The FOX genes pathways functions and ATPase with COX oxidative processes are for producing the four kinases gps are firstly regulated by ATPase for producing four kinases gps then followed by mitochondrial enzymes effects for producing three fatty-acyl-CoA- isoforms started by OPA1 synthetase enzymes effects - gamma-oxidation) for producing fatty-acyl-CoA-synthetase (gamma-subunits) , that their proper activities are related to and depending on the presence of purines in specific sequences with pyrimidine for hydrophobic amino acids acids synthesis where some of those necessary amino acids are:

Alanine amino transferase for Alanine (GCC, GCA, GCG) | for migrating moleculea and the synthesis of mTORC1 (P-S/T-Cytosine kinases) |, related to Arg (AGA , AGG ) | which is necessary for ATPase and GTPase synthesis and reactivities | , related to Ser (AGT, AGC ) | which is necessary for both cytosine kinases and thymine kinases synthesis | , Thr , leu, | which is so necessary for sestrin synthesis and brain activities | and related to Tyr amino acids synthesis (which considered hydrophobic amino acids and imp for regulating most of active subunits and genes ), where the purifications and synthesis of purines nucleotides (guanine and adenosine) in FOX pathways is considered as the TCA cycles which is a part from FOX genes activities for producing two kinases adenosine kinases and guanosine kinases which are firstly regulated by ribosomal oxidative (ATPase) process and COX oxidations for analyzing pro-nutrient-TOR for producing the ribosomal polypeptides kinases (or lipo-poly-peptides kinases) which have the advantages of the Containments of necessary purines for the next steps of the mitochondrial OPA1 synthetase effects (gamma-oxidations) for necessary pyrimidine nucleotides synthesis where the cytosines and Thymine synthesis are regulated processes by OPA1-synthetase enzymes for full
regulating the pyrimidine synthesis for hydrophobic acids production (by gamma-oxidation upon synthetase effects), so I consider that synthetase enzymes is a part from OPA1 sequences that can start adopting and regulate TCA cycles (after the first effect of ATPase) which is a part from FOX genes activities for producing purines kinases which will be joined the pyrimidine production from synthetase effects on lipo-nutrients molecules for hydrophobic acids synthesis within the produced kinases chains subunits (eg S6K1, and other cytokines productions upon the effects of synthetase enzymes).

TCA cycle metabolites in particular, are centrally important determinants of macrophage metabolic re-programming [3].

It has been reported that Metabolism in immune cells is no longer thought of as merely a process for adenosine triphosphate (ATP) production [4], but I reported that ATPase productions are so necessary for all cells specifically immune cells for activating their ATPase productions for creating their necessary active signals transmission for stimulating other cellular biosynthesis and bio-activities which started by the formation of S6K1 peptides which is regulated by P-S/T-Adenosine-kinases and by P-S/T-Guanosine-kinases subunits, and by mTORC1 together productions and can be stored in ribosome as S6K1 which upon phosphorylations will produce ATPase and GTPase that will be directed for repairing OPA1 inner membrane and then will activate the mitochondrial OPA1 synthetase for gamma-oxidation for producing proper necessary gamma-subunits or fatty-acyl-CoA-gamma for Beta-subunit productions upon the synthase effects through beta-oxidations. Where, the death of living cells started by broken ribosomes or mutated RNAs without repair and without producing ATPase or GTPase that will lead mutations or stopping producing acyl-CoA isoforms that can reflect Brocken pathways in TCA cycles and in FOX activities that will stop releasing PSTGk and PSTAk cytokines upon ATPase and COX enzyme oxidative processes that will lead to cells death or pathogenic symptoms.

Also, not that. Tubulin acetylation which regulated by ATPase plays important role in cellular activities including cell polarities that tubulin acetylation forms ATPase and GTPase and depending on ATPase with GTPase productions that reflect healthy status of living cells.

S6K1 synthesis and functions can controls tubulin acetylation (due to S6K1 is main regulator active peptides for ribosomal repairs and ATPase productions), hence S6K1 active subunits are contributing to the autophagic flux induced by different stress conditions and in different cells.

During tubulin acetylation, S6K1 contributes to the flux of autophagy induced by different stress conditions and in different cells, where, this effect appears to be independent of the kinase activity of S6K1. [5]

That S6K1 has the basis of the synthesis from the two kinases (PSTAk and PSTGk) with the regulations by mTORC1, where their synthesis produced from TCA cycles which is part from FOX functions. That
after the two kinase peptides productions (which depends on ATPase phosphorylation) will be modified by mTORC1 for producing S6K1 that can reflect creations of signals effective transmission which will stimulate gamma-oxidation which proceeded by the effects of OPA1 synthetase for producing amino-acyl-CoA-synthetase (gamma-subunits) with enough energy that simplified in the created active signals which used for migrating the produced subunits and stimulating the beta-oxidations.

**Figure 1.** S6K1 synthesis regulated by mTORC1 + P-S/T- Thymine kinases productions bonded with purines which produced from TCA Cycles.

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The effects of OPA1-synthetase (OP1Stase) will be the results of pyrimidine synthesis including cytosine and active signals transmission which will be used for mTORC1 (PSTCk) subunits productions which will be necessary for regulating the biosynthesis of the S6K1 peptides, then those S6ks will be directed for inner cells for repairing and re-activating rRNAs and for ATPase and GTPase productions for mitochondrial OPA1 membrane repairs (OPA1 inner genes) and for the production of acyl-CoA isoforms upon OPA1 enzymes effects which started by acyl-CoA-synthetase (gamma-subunits) by gamma-oxidation, which are so necessary for controls tubulin acetylation’s and for regulating axon growth through beta subunits productions by beta-oxidation followed by alpha-oxidations which produce alpha subunits for axon growth and autophagy biosynthesis.

So, the conversion of glutamate to glutamate is imp reversed the acetylated tubulin-NKA complex, and is so imp for proline synthesis regulated by TCA cycles.

Figure 2. Effects of deficiency of Ser-amino acids in asthma diseases & leads to other diseases symptoms.
After, ATPase Effects started on pro-nutrients-mTOR and the beginning of the formation of S1, 2,6-Kinases. Which can be considered as a variety of cytokines with different compositions or as variety of kinases peptides where their composition is from amino acids differ which their functions of activities depends on their Containment from the purines (qualities and quantity) and their Containment from pyrimidines which started by mTORC1 activities (PST-Cytosine-kinase, then at mitochondrial-synthetase site effects will continuing the thymine purifications and resynthesis necessary hydrophobic acids) on S6K1 production, then S6ks will be stored in cells and adipose tissues as lipo-S6K1 peptides which also can be considered as lipopeptides kinases or cytokines with different compositions from. Purines and pyrimidine which after storages will be needed to be modified and reactivated through the mitochondrial OPA1 enzymes oxidations (due to and during stress and stimulating muscles activities) for reproducing fatty-acyl-CoA-synthetase subunits (gamma oxidations) which considered as the remaing recovery step for recreating pyrimidines for hydrophobic acids synthesis and creating the needed active signals transmission enough for binding those active pyrimidine to original purines in their lipo-peptides chains for amino acids synthesis through producing full fatty-acyl-CoA-synthetase subunits, which will follow the effects of synthase oxidations (beta-oxidation) for reproducing the needed anti-inflammatory subunits Beta-subunit (fatty-acyl-CoA-synthase) where their composition depending basically on the primary gamma-subunits compositions.

The mammalian target of rapamycin (mTOR) positively regulates axon growth [6],

Where, mTORC1 is the substrates (the basis for regulating S6K1 peptides productions) of regulating and stimulating ribosomal S6-protein-kinase-1 (S6K1) synthesis through Fox Serine/Threonine signalling activated pathways in response to nutrients and growth factors.

And the maintaining of glucose supply for protein synthesis (S6K1) is necessary for central nervous system and for the formation of the three acyl-CoAs (isoforms) for fatty acid synthesis [7]. The maintaining of glucose supply (purines supply) is necessary too for reactivating the long fatty acids chains productions upon ATPase effects and COX effects, and for S6K1 synthesis which necessary for controlling platelet activation and aggregate formation [8].

Maintaining glucose supply(purines supply )are necessary for ATPase reactivation through regulating S6K production (with proper composition from hydrophobic amino acids eg of proline, ser, Arg, Leu and tyrosine) which is necessary for reactivating GTPase synthesis which is necessary for reactivating OPA1 membrane enzymes which are necessary for ROR-gamma, ROR-beta and ROR-alpha active subunits biosynthesis, for glucocorticoids three isoforms productions, and for the three interferons (IFNs) isoforms productions gamma, beta and alpha respectively.

The availabilities of proline (Pro), Arg, Gly, Asp (GAC), Ser, Thr, Leu, and Tyr amino acids are so necessary for S6K proper peptides which enhance the proper functions of ATPase and OPA1 oxidative
processes (Gamma, beta, then Alpha) which can analyze tumors, coagulation, prevent platelets aggregation, prevent bones weaknesses and erosion of the vertebrae, and prevent diseases symptoms. But Asp (GAC) is necessary for deliver its purines A&G by cytosine to endocytic ribosomes (where, Cytosine imp for tRNAs productions and for deliver molecules), where A&G are the only necessary purines for ribosomal repairs, for ATPase, and for GTPase synthesis where the GTPase is so necessary for mitochondrial proper OPA1 inner membrane repairs for generating the OPA1 outer membrane.

The proper ATPase composition is necessary for amphetamine-based anorectic which necessary to maintain neuronal excitability which can rapidly converted into amphetamine in vivo. Na+, K+-ATPase which is a membrane-bound (MBE) enzyme that can maintain signals activities and maintain Na+, K+-ATPase for brain activities [9].

Where, Na+, K+-ATPase (MBE)is aoptong hypertension, where, The N'A, K, ATPase functions is stabilizing cellls membranes signals transmission activities and adopt the -ve charges signals transmission that can adopt and stabilizing brain activities.

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Also, Stimulation of Na (+), K (+)-ATPase activity (which basically depending on the S6K1 biosynthesis) increases sodium transport across the renal proximal tubule epithelia,[10].

What is the relation of S6K1 to high blood glucose (hyperglycemia) or low blood glucose (hypoglycemia) and diabetic coma? We begin that diabetic disease include either hyperglycemia or hypoglycemia but we should not describe diabetes according to hyperglycemic or hypoglycemic but those phenomena reflect the Consumption, cracking and loss of ATPase in biological processes without normal repairs or can be repaired but with mutated characters with sever deficiency in pyrimidine nucleotides in S6K1 peptides which is the basis of ATPase synthesis, that (as I mentioned before) the deficiency in Ser amino acids during FOX functions will lead to decreasing in the PSTTK and in PSTCK kinases and will lead to androgren instead of estrogen that will include mutated S6K1 peptides with deficiency in pyrimidine in their subunits chains that reflect deficiency in hydrophilic acids in S6K1 peptides, that S6K1 will be directed to inner cells for producing mutated ATPase which describe as rich of purines with lacking pyrimidine.

**Figure 4.** Roles of estrogen for glucocorticoids synthesis, While Androgens cannot promote GCs synthesis but through feedback can promote S6K1 synthesis.

As mutated ATPase started for performing its activities will firstly start to consume its own purines without compensation that will lead to increasing in blood glucose without catalyzing or functioning which describes as hyperglycemia.

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But hypoglycemia is the phenomena that describe increasing in mitochondrial oxidative processes with decreasing in ATPase biosynthesis (may at the early stages of diabetic Symptoms), that may at early stages of diabetic diseases there are enough ATPase for performing the catalysing of sugar molecules but without ATPase repairs that later will be turned to hyperglycemia.

Diabetes is the result of a deficiency in Ser amino acids that reflect deficiency in the formation of the kinase PSTTK and PSTCK (mTORC1), which reflect a decreasing in the formation of pyrimidine nucleotides during FOX activities during pro-nutrients-mTOR metabolic pathways, which leads to the decreaseing in the production of estrogen then will be replaced by androgens, synthesis where androgen describe as rich of purines (Adenosine and Guanosine).

So during S6K biosynthesis with deficiency in Ser amino acids will produce a mutated S6K1 peptides with rich of purines and deficiency of pyrimidines that when first regulate ATPase productions will produce mutated ATPase without normal repair that when the mutated ATPase began its activities will start to use their Containments from adenosine and guanosine for catalyzing pro-nutrients-mTOR molecules for producing LPS and long fatty acids chains, that ATPase will spend and consume all of its A&G purines nucleotides that will be broken completely without normal repairs with depends on Ser availability on the production of psttk and PSTCK (mTORC1) during FOX activities, that will not stimulate the mitochondrial enzymes activity, which leads to shivering in the body and may diabetic coma due to the loss of and consuming most of ATPase without normal repairs and recovery, and due to the lack of mitochondrial reactivation.

Antibodies are immunoglobulins proteins which can be classified into ribosomal and non-ribosomal peptides and differentiate according to their amino acids Containments (quality and quantity) , where non-ribosomal peptides that didn’t follow the roots for soluble MHC class II synthesis for running endocytic necessary roots functions (as TLR4 synthesis for Plasma membrane synthesis), and still not modified by OPA1 enzymes activities for producing proper active cytokines with proper composition from hydrophobic amino acids. Some antibody consists of four or five polypeptides that each Can described as carry the compositions of one of protein kinases that produced from pro-nutrient-mTOR -FOX Ser/Thr Signaling pathway which produce four types of protein kinases as described before.

Each of those antibody peptides when oxidized by OPA1 enzymes will give more optional for generating the three fatty-acyl-CoA isoforms gamma, beta and alpha subunits, that alpha contain alpha, beta and gamma, but beta contain beta and gamma, but gamma contain only gamma subunits, where those acyl-CoA isoforms subunits are necessary for regulating macrophages and T-cells biosynthesis and consequently necessary for myeloid and lymphoid cells activities for proper SIRPα productions for MHC class-I synthesis which promote the endocytic MHC class II synthesis.
Those necessary acyl-CoA three isoforms can be functioned directly by OPA1 regulations for glucocorticoids and for the three interferons isoforms re-synthesis, then for SIRP- which will be for MHC class-1 which regulate endocytic soluble MHC class II synthesis for TLR4 re-synthesis endocytic roots of activities. insulin has two chains A&B that A and B chains become linked together by two sulfur-sulfur (disulfide) bonds. Pro-insulin, insulin, and C peptide are stored in granules in the beta cells to be released in capillaries [10],

The two A&B chains are considered as two kinases protein one is "A"formed from Ser and the other "B" is formed from Thr amino acids through breaking its nucleotides during and through pro nutrient-mTOR-Fox Ser/Thr Pathways which regulated by ATPase and Cox enzymes. But one of them nearly "B" chain is poor of pyrimidines Containment but rich of purines (that has the ability to recover S6K1 for recovering ATPase and GTPase), while the other chain "A" is rich of pyrimidines (Thymine and Cytosine) were, both subunits chains are bonded with sulfur=sulfur bonds within beta-cells for beta-cells functions and secretion.

Immune consists of two types of lymphocytes: T and B cells, that T cells can produce a large number of cytokines through feedback upon the activity of MHC class-I which include and involve synthetase activities, where B cells require specific differentiations and activation conditions to produce cytokines [11]. the beta cells can only produce only kinds of cytokines (as i refered in previous lines of words) the 1st cytokine is the PS/T-Thymine Kinase and PS/T-Cytosine kinase from "A"chain while B chain produce PS/T-Adenosine kinases and PS/T-Guanosine kinases which can Switching the production of antibody isotypes in B cells, differentiation of helper T cells which regulated by cytokines [12].

Cytokines are peptides kinases that formed from Ser/Thr -FOX signaling activities regulated by ATPase and Cox then by OPA1 enzymes functions for the three acyl-CoA isoforms productions.

B chain is has the function of recover S6Ks peptides production depending on the availabilities of amino acids composition and their cosequences which can be regulated firstly by ATPase sequences arrangements that are firstly be modified throughout TCA cycles (which is part from FOX and pathways) and through mitochondrial OPA1 enzymes for producing antibodies peptides which can be classified to three types of antibodies depending on their Compositions from amino acids and fatty acids:

1, type AB-gamma

2, type AB-beta

3, type AB-alpha

First AB gamma which include synthetase can analyze and destroy beta cells if their "A" chain is absence (in specific cases depending on their Containment from amino acids and depending on continuing of
gamma-oxidations) and hepatic cells, but AB-beta activate Beta-cells and IFN-beta and can protect hepatic and beta-cells and can increase anti-inflammations processes (through beta-oxidations regularity), but AB-alpha can be started to be activated through AB-beta upon effects of phospholipase for accelerating SIRP a myeloid for MHC class-I productions which produce endocytic MHC class II which is responsible for producing the endocytic TLR4 synthesis that regulate plasma membrane synthesis and run proliferations processes.

When, pyrimidines decreased in nutrition in vivo, the AB-alpha will be enhanced by both synthase and synthetase specifically last one synthetase for reactivating gamma-oxidations for reactivating pyrimidine synthesis for hydrophobic amino acids synthesis for recover the "A"chain Which regulate "B" chains in insulin and in beta-cells, and that eill need the reactivating of beta-oxidation (after first Gamma-oxidations completed) for Beta-subunit synthesis for B-cells, for GC production, for IFN-beta production, and for alpha-subunits production upon the phospholipase effects on Beta-subunit. The alpha-oxidations is the necessary processes needed for proliferation including SIRPα1 productions which necessary for TLR4 synthesis and regulations.

B lymphocytes (B-cells) can activate a type of white blood cell through the of stimulations beta-oxidations by OPA1 synthase (which rich of pyrimidines in hydrophobic acids) where first stimulation started from gamma-oxidation which generate signals that will stimulate followed and dependent OPA1 oxidations.

A chain (rich of pyrimidines) in beta-cells are specified for stabilize, and regulate B chains while B chains had the function of regenerate S6K1 subunits (and vice-versa where both B chains and S6 are characterized by their rich of purines and regulated and stabilized by A chains) for adopting the balance of ATPase, GTPase, and endocytic ribosomal activities.

It has been reported that preventing hepatic insulin resistance via the adenosine monophosphate-activated protein kinase-p70 ribosomal S6 kinase-1 pathway. [13]

Indicating that the generations of PSTGk PSTAk, PSTCk and PSTT-K inase are the basic for AB chains production but B chains are specified for hormones growth regulated by A chains regulated by OPA1 enzymes, and are the badis to prevent insulin resistance.

S6K1 is necessary for insulin growth that as i mentioned befor the protein kinases that responsible for S6 productivity through Ser /Thr- nutrient-mTOR-FOX signaling pathway are PS/T-Adenosine kinase and PS/T-Guanosin kinases which are created from mainly Thr amino acids that are rich of purines that are used for S6K1 synthesis then for both ATPase and GTPase, where, S6K1 can activate insulin growth and vice versa.

That, the insulin-induced activation of p70 S6 kinase and MAP kinases. [14]
Also, the Containment of hydrophobic amino acids in S6K1 and in the four kinases produced from Ser/Thr -mTOR-FOX signaling pathways are do necessary for determining the advantages of the produced insulin activities in vivo.

That amino acids are necessary for the insulin-induced activation of mTOR/S6K1 signaling and protein synthesis in healthy and insulin resistant human skeletal muscle [15]

The insulin and drugs resistance occure due to Fixation of dpecific fragments of amino acids in subunit due to increasing in +velinkages that stabilize linkages against antibiotic or against OPA1 oxidative processes which have to be occured for renewal Brocken amino acids and broken necessary linkages for continuing adopting the necessary molecular structure for proper endocytic processes and for proer adopting final immune efficiency and anti-inflammatory processes. So The resistance to antibiotics occurs due to deficiency in Ser/Thr-mTOR-Fox pathways that reflect decreasing in S6K1 production consequently decreasing in ATPase and GTPase, decreasing in RORs synthesis pathways, deceeding in gamma, beta, and alpha-subunits productions upon gamma, beta, and alpha-oxidations respectively upon synthetase, synthase, and phospholipase oxidations respectively, and deceeding in fatty-acyl-CoA isoforms productions too.

The Containments of specific advantages amino acids in gamma, beta, and alpha active subunits can accelerate proper ATPase activities and OPA1 oxidations eg :Proline, ser/thr, and hydrophobic amino acids playing important roles in MHC-class-I when regulate the endocytic MHC class II synthesis which regulated TLR4 synthesis and TGF-gamma/beta/& alpha synthesis respectively, where the presence of proline in IFN-gamma, in GC-gamma , in TLR4 genes and in IFN-beta will accelerate oxidative OPA1 anabolic processes and then accelerate the alpha oxidations for MHC class II productions for SIRPα1 synthesis which necessary for TLR4 production and for TGF-alpha productions respectively and then for the direct the flow of endocytic biological processes for proper proliferations of plasma-membranes, collagen synthesis and blood platelets, [16]

CD8 T cells as well as other cells can and do produce IFN-γ during M. tuberculosis infection. Jan [17].

**S6K1 consider as protected basic subunits for Interferons (IFNs) isoforms synthesis regulated by pyrimidine-kinases:**

It has been reported that interferons are a family of cytokine mediators critically involved in alerting the cellular immune system to viral infection of host cells. [18]

But, firstly I need to report that interferons aren't a family of cytokines where cytokines which produced by pro-nutrients-mTOR-FOX activities pathways through ATPase regulations are just four gps of

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cytokines kinases which will be affected by the mitochondrial three anabolic enzymes in regulated arranged orders for producing firstly the fatty-acyl-CoA-gamma which will be affected by synthase enzyme for producing fatty-acyl-CoA-beta which then will affected by phospholipase as a 3d step for producing the fatty-acyl-CoA-alpha, where those three fatty-acyl-CoA-isoforms will follow their necessary cellular pathways for producing firstly the three glucocorticoids-isoforms which have the functions for producing three interferons isoforms, where both Glucocorticoids and interferons are having the characters and advantage of recovering each other’s in the advantages of their proper Containments from proline, Ser, Arg, Tyr, Leu and other necessary hydrophobic amino acids for their necessary activities as modulating the anti-inflammatory molecules production, so in other meaning: glucocorticoids and Interferons (beta and alpha) are the first initiation of anti-viral to innate immune modulators to be characterized as anti-inflammatory.

Secondly, interferons are not alerting central immune to viral infections, but interferons are produced for modulating the anti-inflammatory synthesis (not alerting original basic genes and subunits) as necessary active subunits that produced through the regulation of ATPase and OPA1 three enzymes for modulating and re-modifying the cytokines and S6K1 peptides (if necessary) for the three fatty-acyl-CoA-isoformes productions for glucocorticoid isoforms biosynthesis, and for Interferons isoforms synthesis, where both IFN and GC are sharing together the anti-inflammatory processes with each other and are having the character for recovering each other’s.

Also, the meaning of alerting means completely change in the bases of immune basic subunits and genes which are basically fully related to the compositions of a specific chromosomal active sequences and to ATPase enzymes compositions, where, also ATPase are fully related to the S6K1 peptides compositions too, but interferons according to ATPase composition will be stimulated for modulating and modifying immune anti-inflammatory subunits productions for modifying and strengthen specific kinases for anti-viruses and anti-toxic tools functions through the mitochondrial OPA1 regulations.

Ribosomal peptides S6 kinase beta-1 (S6K1) is a product of serine/threonine kinase of the mechanistic target of rapamycin (mTOR) \((\text{pro-nutrients-mTOR-FOX})\) pathway, that has imp roles in immune regulating or promoting the lymphocyte activations through firstly regulating ATPase repairs and productions, then through reactivating mitochondrial OPA1 gene repairs by GTPase productions, hence S6K1 has imp roles in glucocorticoid-isoforms and in interferons-isoforms productions and activities (through ATPase and GTPase synthesis) thus has an basic roles in regulating lumphocytes activities, where

S6K1/S6 axis participated in the primary response of anti-bacterial adaptive immunity in Nile tilapia [19].
And, Interferons-Dependent Engagement of Eukaryotic Initiation Factor 4B via S6 Kinase (S6K)- and Ribosomal Protein S6K-Mediated Signals [20].

The mRNAs translation for IFN-sensitive clearly are the S6K1 peptides that activate ATPase phosphorylation which back phosphorylate the eIF4B on Ser amino acids for adopting IFN gamma, beta, and alpga compositions through translations according to primary S6K1 Containment and then related to ATPase sequences composition and its Containment from well-arranged amino acids.

Where, any mutations occurs in S6K1 peptides due to absence of Ser, Arg, proline, Thr, tyr or leu or due to absence of normal percentage of pyrimidines in active kinases or active suburbs or genes can reflect types of pathogenic symptoms.

Eg: The deficiency in Arg amino acids in S6K1 will reflect decreasing in OPA1 oxidative processes and mutations in IL-beta subunits "long fatty-acyl-CoA-synthase" (GC or IFN) which will promote mutated TLR4 (gamma, beta) synthesis, which will promote linear mutated TLR4 production for proliferations which will characterized by deficiency in GTPase and deficiency in citrulline productions which normally done by catalyzing Arg amino acids for producing GTP-CHase enzyme and citrulline (which consider as the basis for Erythropoietin productions, and for Plasma membrane synthesis), hence deficiency in Arg will lead to deficiency in plasma membrane synthesis and function, deficiency in mitochondrial OPA1 inner membrane repairs, deficiency in brain activities and deficiency in liver functions too that can lead to decreasing in the fatty-acyl-CoAs migrations and decreasing in active signals transmissions ...

The re-activation of proper ribosomal protein S6 kinase 1 (S6K1) will activate digestion of pro-nutrients-mTOR molecules during FOX signaling pathway aspects of increasing caloric energy through reactivating ATPase with GTPase property for reactivate OPA1 inner membrane repairs and promote signals transmission activities which re-promote mTORC1 and Thymine kinases activities pathways for reactivating tRNAs and leu with Tyrosine metabolic pathways to achieve healthy longevity.

Asthma is characterized by Prediabetes and diabetes, that reasons of occurrence the two disease are same:

It has been reported that (S6K1) inhibition with rapamycin inhibited IFN- and EGF-induced protein synthesis [21]. In Severe asthma which characterized by increased airway smooth muscle (ASM) that begin due to decreasing in Ser amino acids in pro-nutrients-mTOR-FOX pathways that will reflect decreasing in the PS/T-Cytosine-Kinases (mTORC1) and in PS/T-Thymine-Kinases production (which are necessary for migrating and regulating molecules too) with increasing in Adenosine-kinases with Guanosine-kinases (which are specified for S6K1 peptides synthesis) that will lead to decreasing in migrating molecules and decreasing in tRNAs with increasing in ATPase and GTPase (which originally

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and repaired and reactivated by S6K1 peptides) that will lead to promote glucocorticoids and interferon synthesis characterized by deficiency in Ser amino acids and in the same kinases (PSTCK and PSTTK) productions, that will lead to decreasing in sugar, lipid, and carbohydrate metabolism (increasing of purines molecules and LPS in blood and interstitium fluid) conjugated with increasing in S6K1 peptides productions (for ATPase repair) and for growth factor synthesis, that will lead to increasing in airway smooth muscle (ASM), note, those patients are having the so high risk of sever diabetic problems due to deficiency of Ser amino acids in pro-nutrients-mTOR-FOX signaling pathway that will lead to deficiency in estrogen production with increasing in androgen production which are characterized by high purines with deficiency in pyrimidines nucleotides (deficiency in pyrimidine-kinases which are PS/T-Cytosine Kinase and PS/T-Thymine kinases), also the pyrimidines-nucleotides will disappeared in S6K1 peptides chains, consequently will lead to deficiency of pyrimidines (Thymine and Cytosine) in ATPase and in GTPase, that will cause mutations (pyrimidines deficiency) in the productions of long fatty-acyl-CoA-isofomres upon OPA1 enzymes oxidations.

So, positively Asthma is characterized by diabetes symptoms May in the early days of Asthma cannot be detected but later can be detected. Where, there are limited data on the risk of pulmonary disease in patients with diabetes [22].

And, It is concluded that asthma and T2DM are two common chronic conditions of increasing prevalence and that often coexist in the same patient [23].

Also, it has been reported that: Prediabetes and diabetes have been recently identified as risk factors for asthma exacerbations in adults [24].

Note, decreasing in Cytosine-kinases and or fatty-acyl-CoA-synthetase (gamma-subunits) will reflect decreasing in ATPase repairs and re-activities that lead to accumulations of subunits within cells and in the interstitium fluid that lead to decreasing in their migration with increasing in their +ve bonding energy that lead to tumor cancer and can reflect early other diseases symptoms eg: early diabetic symptoms.

Where, Advances along the small GTPase front have implicated cell migration [25].

Proper GTPase productions implicate cell migrations and the mitochondrial OPA1 membranes repairs in case of availabilities of both PS/T-Cytosine kinases and PS/T-Thymine Kinases (and in availability of proline and hydrophobic amino acids that accelerate OPA1 anabolic oxidative processes properly) that can increase Tyrosine metabolic pathways and will increase signals transmissions that will promote the migrations of active genes and subunits which can activate beta-oxidative processes and alpha-oxidations (that regulated by synthase and by phospholipase respectively), that can promote phosphatidic acid (PA) to re-binds to mTOR and to re-binds to S6K peptides independently of mTOR,
where S6K peptides synthesis are basically depending on the two purines kinases that produced from Ser/Thr-FOX signaling pathways for producing PS/T-Adenosine k and PS/T-Guanosine kinases for S6K1 synthesis, for ATPase and for GTPase reactivities, and for promoting endocytosis MHC class II functions, where its migration need the availabilities of Cytosine-kinases and Thymine-kinases (active pyrimidine-kinases) production for S6K1 peptides productions and for tRNAs synthesis.

**MHC Class-I is fatty-acyl-CoA gamma-subunits (IFN-gamma) for modifying their fatty acyl-CoA-beta (IFN-beta) synthesis to be site and lie on nucleated cells as MHC class-1:**

The IFN-gamma is regulated by the effects of synthetase on long-fatty acids chains (gamma-oxidation) for producing fatty-acyl-CoA-synthetase subunits (IFN-gamma) that has the function to activate the endocytic MHC class II synthesis which originally produced from MHC class-I which originally act on inflammations and on infected cells to bind to selected peptides then migrate to nucleated cells to site and lie on membrane for producing endocytic MHC class II.

The biosynthesis of long fatty-acyl-CoA-synthetase (ACS) and its other two CoA-isoforms (ACISF) beta and alpha are acting as homodimeric enzymes, that acyl-CoA synthetase member 6, ACSL6, is a form present in the plasma membrane of cells. [26]

Where, "ACS" productions are necessary for regulating TLR4 which necessary for plasma membrane synthesis, and necessary for endocytic MHC class II synthesis started by fatty-acylCoA-gamma which act on inflammations to bind to their peptides which will be filtered through cells membranes for the endocytic MHC class II synthesis where necessary soluble amino acids rich of purines molecules will pass through membrane (leaving the MHC class I sitting on nucleated cells membranes )for creating MHC class II.

The function of MHC class 1 (which consist of long fatty peptides of long fatty-acyl-CoA-synthetase sequences) ACS is to analyze pathogen inflammation then bind to analyzed peptide fragments derived from pathogens inflammations then display them on the cell membrane for filtration through for recreating the soluble endocytic MHC class II. The consequences of MHC class 1 are deleterious to the pathogenic infected cells where MHC-I contains the fatty-acyl-CoA-synthetase that able to analyze inflammation and infected cells for binding to their peptides for creating endocytosis soluble MHC class II , where the remaining from MHC class-I on the surface of cells membranes can reproduce IFN-gamma then IFN-beta and cytokines for reactivating pro-nutrients-mTOR -FOX pathways regulated by ATPase and OPA1-synthetase for recycling immune adoption eg of B cells which produce antibodies upon reactivation os fatty-acyl-CoA-synthetase that can analyze or neutralize extracellular pathogens through
promoting IFN-gamma for analyzing inflammation and activate the pyrimidine synthesis (for modifying IFN beta) followed by IFN-beta productions upon synthase effect on IFN-gamma.

The MHC class-I can looks like varies in their its composition but MHC class-I contain of fixed stable characterized fatty-acyl-CoA-synthetase (gamma-subunits) active sequences that has the function of analyzing inflammation and infected cells which can bind to the analyzed peptides for resitting and display them on cells membranes for recreating the soluble endocytosis MHC class II production.

IFN-gamma has the functions of anti-inflammatory processes that can analyze inflammation and infected cells for binding to resulted peptides and recreate pyrimidine (the function of synthetase) for modifying its own active gamma-subunits and then for regulating IFN-beta synthesis upon the effects of OPA1-synthase enzyme, that has been described as exerting a growth factor and tool activity through reactivating the endocytic TLR4 upon phospholipase and MHC class II mediate or directly active the previous TLR4 activity that stimulate normal T lymphocytes, that can activate T-cells and macrophages and vice versa.

Furthermore, the co-expression of MHC class II molecules and TLR2 or TLR4 in human embryonic kidney (HEK) cells 293 leads to enhanced production of the anti-microbial peptide human-β-defensin. [27] Previous study indicating the imp fact that MHC class II enhance the endocytic TLR4 reactivities upon phospholipase oxidative effects. Where, MHC-II molecules are important for initiation the antigen-specific immune response where need to be promoted by activating TLR4 for endocytic proliferation then for external proliferations.

Dendritic cells (DCs) initiate adaptive immune responses by activating T cells via cognate interactions between MHC-peptide complexes and T cell receptors.[28] where, class II is predominantly stored in endocytic plasma membrane, where it has a short half-life because of its regulation to TLR4 synthesis for Plasma membrane modification and re-synthesis, that is why the plasma membrane which promoted by MHC Class II and formed by TLR4 its Containment is MHC class II.

And it has been consedered that T cell growth-promoting activity of interferon-gamma.[29]

And also, IFNγ mediates CD8 T-cell cytotoxic function. that in vivo, antigen-specific CD8 T cells that produce INFγ necessary to effect rejection of skin grafts. [30]

Where, cytokine production upon FOX activities will be modified by the effects of mitochondrial enzymes to produce specific modified IFN-gamma which has the anti-inflammatory effect and binding to selected of result peptides that will reactivate IFN-beta upon synthase oxidations and then will site on and cover neucleaed cells for MHC class II synthesis which will has the role of reactivating TLR4 upon regulation of phospholipase for Plasma membrane synthesis and for TLR4 other functions.

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Also, the ability of CD8 T cells to re-produce IFNγ indicating that IFNγ connected to the MHC class II re-activities, and in fact as i mentioned above that IFN-γ basically has the function of regulating the MHC class II synthesis that during inflammation and infection the IFNγ will analyze inflammations content through gamma-oxidation then will bind to selected resulted peptides for modifying its own subunits then will sit and lie on cell membrane as MHC class-I for reactivating the endocytic soluble MHC class II synthesis.

Also, i would like to mention that i considered MHC class II is a fatty-acyl-CoA-synthase (Beta-subunit) Which regulate and activate TLR4 synthesis upon phospholipase oxidations for producing fatty-acyl-CoA-phospholipase (alpha-subunits which considered as IFN-alpha necessary for proliferation cycles).

That the interferons (IFNs) have functions and diverse effects upon OPA1 oxidations on initiate and adapting immune cells during infection including proliferations function through regulating TLR4 for running proliferations.

In conclusion the previous studies indicated that MHC class-I considered as fatty-acyl-CoA-synthetase (gamma-subunits) and considered as IFN-gamma that can analyze infected cells and inflammations then bind to their peptides for modify and promote IFN-beta synthesis upon synthase oxidations covering nucleated cells membranes for reproducing MHC class II which cobsidered as fatty-acyl-CoA-beta (IFN-beta) that upon alpha-oxidations will promote fatty-acyl-CoA-phospholipase which considered IFN-alpha for regulating TLR4 synthesis upon the same alpha-oxidations for plasma membrane synthesis which contain MHC class II, and then again act on inflammations and on infected cells through feedback for re-producing IFN-beta then IFN-gamma regulated by OPA1 oxidations across cells membrane for acting on inflammation and bind again to their peptides for re-improving their gamma-subunits and Beta-subunits (which conclude gamma-subunits in their chains) which can re-modified again and act as MHC class-I which will re-sit and lie on cells membranes for running the soluble endocytic MHC class II synthesis and then TLR4 synthesis, where I consider that the endocytic soluble MHC class II synthesis as the first stepes for modifying immune cells followed by TLR4 synthesis for adopting immune including brain for anti-inflammatory responses.

Where, Thr, Gly, Glu, Arg, Lysine-rich proteins (AAG, AAA) are the most important amino acids peptides for rebuilding necessary fatty-acyl-CoAs isoforms (IFN-isoforms) and for necessary MHC class II that can be stored in lysosomes, for running OPA1 oxidative processes and for TLR4 synthesis to perform proliferations, for adopting neurons response, and for promoting brain cells functions, where MHC class II is regulated by MHC class-I synthesis and its Containment from hydrophobic amino acids which are characterized by their active pyrimidines contents which can accelerate OPA1 oxidative processes, eg: the availability of Arg and proline which are having the advantages of functions of accelerating OPA1...
oxidative processes for purines productions which necessary for rebuilding MHC class-I which controlled and regulated by pyrimidine synthesis.

On the other hand, the Tyr, Met, Arg, Ser, Pro, and Leu amino acids are so necessary amino acids for rebuilding the proper MHC class-1 which can regulate and promote MHC class II synthesis which regulate TLR4 synthesis for endocytic plasma membrane synthesis.

Signal regulatory protein α SIRPa (which SIRP-gamma) is the basic for producing IFN-beta then IFN-alpha which activate TLR4 for Plasma membrane synthesis where through feedback will produce firstly MHC class II (IFN-beta upon synthase beta-oxidation) followed by gamma-oxidation for producing MHC Class-I:

Signal regulatory protein α (SIRPa), also known as Src homology 2 domain-containing phosphatase substrate-1, is expressed on myeloid and hematopoietic stem cells and neurons. Where due to SIRPa activities it can increase signals transmissions that will increase migrations, OPA1 oxidations, and cell proliferation, and transformation.

SIRPa is basic for producing IFN-alpha and TLR4 that through feedback will produce firstly endocytic MHC class II and IFN-beta (SIRP-Beta) upon synthase beta-oxidation, then followed by MHC Class-I and IFN-gamma productions (also considered as SIRP-gamma) upon synthetase oxidations that will sit and lie on nucleated cells membranes ready for acting on inflammation and on infected cells and running their external roles of anti-inflammatory functions and internal endocytic activities.

Signal regulatory protein α negatively regulates mast-cell activation [31].

And Ligation of SIRPa (on macrophages) by CD47 (on RBCs) promotes tyrosine phosphorylation [32].

SIRPa is negatively regulate mast cells directly (indicating SIRPαhpa is not alpha subunits which has phospholipase effects ) but can activate mast cells by stem cells (through activating MHC class-1 and class II) , furthermore the SIRP can promote Tyrosine phosphorylation that due to its compositions originally from fatty-acyl-CoA-synthetase that can promote Tyrosine phosphorylation pathways due to it contain synthetase which promote pyrimidine synthesis (Tyr, Leu... etc) that will be phosphorylated through Gamma-oxidations which can be run by IFN-gamma or by GC-gammma and by SIRP-Gamma1 which are depending on OPA1 synthetase enzymes activities .

The IFN-γ-induced surface expression of CD47 contributed to a stronger binding affinity to SIRPa. [33]. Where, IFN-γ have the same active sites that has the specificity for strengthen SIRP-gamma1 for acticate the stronger binding affinity of SIRP and strengthen higher activities in SIRP-gamma.

This study indicates that the two subsets of CD14+SIRPa had limited ability to migrate and phagocytose; but stimulated T-cell function [34].
Where, due to low concentration of CD14+SIRPα (specifically SIRP subunits) can limit migrations but in general SIRP which is SIRP-gamma (and SIRP-beta, and SIRP-alpha which is imp for TLR4 synthesis and back-feed proliferations) has the function of analyzing inflammations and then the results of SIRP-gamma activities is increasing in signals transmission which promote and activating the migrations of molecules and promote analyzing inflammations. 2’-5’-oligoadenylate synthases (OASs), a family of latent 2’-5’-adenylyl transferases, otherwise involved in cellular antiviral responses, are also involved in PAR remodeling of the DDR in MDS and AML cells [35]

Myeloid cells are major players that exploit the regulators of Arginine metabolism (for proline synthesis) to mediate diverse, and adopt immunity [36].

That fatty-acyl-CoA-Synthetase in myeloid is so imp for adopting TCA cycle (Arg metabolism) which has the function of purines synthesis and proline synthesis, and also synthetase control the pyrimidine synthesis for hydrophobic amino acids synthesis Tyr, Leu, Ser, Arg, Pro... etc (which includes both purines and pyrimidine).

In conclusion I would like to declare imp fact that SIRPα is not alpha subunits but is secreted as SIRP-gamma from myeloid and hematopoietic stem cells and neurons (that SIRPα1 has not the ability to activate mast cells ) that is secreted as so active SIRP-Gamma sensor (gamma-subunits) "fatty-acyl-CoA-synthetase" that modified by Arg metabolism that stimulated for acting on inflammations and on infections , that when infections and inflammations started in human induce fast active signals for SIRP-Gamma (IFN-gamma ) productions for acting fast on inflammations and infection-ed cells for analyzing their contents then bind to results peptides for modifying its own sensor subunits and for promoting the productions of SIRP-2-Beta (IFN-beta) upon regulations effects of synthase which will directed to nucleated cells membranes to sit and lie on as MHC class-I which will promote the the endocytic soluble MHC class II which considered ad SIRP-Beta (IFN-beta) synthesis which upon alpha-oxidations by phospholipase will produce SIRPα (IFN-alpha ) which will be directly promote TLR4 synthesis for modifying plasma membrane and for necessary proliferations when upon feedback regulated by OPA1 enzymes will reproduce the MHC class-I on the external cells membranes for further acting on inflammations.

When those nucleated cells lack the endocytic SIRPα (IFN-alpha) and will give the option to SIRP-1-gamma (IFN-gamma) to analyze those cells and resynthesis in case of availabilities of endocytic alpha-oxidations and SIRPα (IFN-alpha) and TLR4 genes which through feedback will produce MHC class II and so on.

Also, the differences in amino acids between the first produced SIRP-gamma subunits and the feedback MHC class-I (the adopted MHC class-I which produced from endocytic MHC class II and from endocytic TLR4) are the necessary amino acids that has to be feed to vaccinated body for running full proliferations
for adopting full immune responses in availability of proper OPA1 for full anabolic phosphorylation oxidative processes for long period of proper vaccine in those tissues.

**The role of the OPA1 oxidations cycles in producing S6K1 for ATPase for producing and functioning the fatty-acyl-CoAs for producing NADH and then ATPase:**

The metabolic purpose of fatty acid oxidation is to generate NADH for ATP generation by the regulations of mitochondrial OPA1 membrane oxidative phosphorylation effects. [37]

FFAs are activated via esterification to CoA, which generates a fatty acyl-CoA moiety [38]

Fatty acid oxidation produces acetyl-CoA units which move in this pathway as fatty acyl-CoA derivatives for utilizing NAD and FAD. [39]

So, When OPA1 oxidations absent will prevent the fatty-acyl-CoA synthesis and then will increase fatty acids accumulations due to decreasing in the OPA1 oxidations and will decrease or prevent the production of NAD and FAD and consequently reduce Vit K metabolic cycle and ATP productivity, that decreasing on ATPase will decrease the lipid, carbohydrate, and protein metabolism through decreasing FOX pathways and then decreasing in ROR-gamma then decreasing in ROR-beta then decreasing in ROR-alpha which lead to decreasing in proliferation and deficiency in immune functions.

The long-chain acyl-CoA enters the fatty acid gamma-oxidation followed by β-oxidation pathway, which produce one acetyl-CoA which is fatty-acyl-CoA-synthase acylCoA-beta. That produce NADH and FADH2 and then the TCA cycle are activated by the electron transport signal transduction which yield from gamma-oxidation processes.

Where NADH and FADH2 produced by both β-oxidation and the TCA cycle are using the electron transport chain to produce ATP. [40]

Nicotinamide adenine dinucleotide, oxidized form (NAD+) where, NAD+ deficiency has been found in models of a number of diseases such as cerebral ischemia, myocardial ischemia, and diabetes, and in models of aging.

NAD+ deficiency is a common central pathological factor in a number of diseases. [41]

So, decreasing or deficiency in S6K1 production will reflect the decreasing in the ATPase which also reflect the decreasing in mitochondrial OPA1-oxidations and decreasing in NAD and FAD that reflect the beginning of many diseases as asthma, diabetes, cancers... etc.

Where, NAD+ treatment has been shown to reduce PARP1-induced astrocyte and prevent PARP1-mediated NAD+ depletion in cardiac myocytes in the presence of H2O2. [42]
NAD is so necessary for MHC class-I synthesis where, The degradation of most cellular proteins occurs by the ubiquitin-proteasome pathways peptides generated by the ubiquitin-proteasome pathway which are presented by MHC class I molecules [43].

So, NAD and proteasomal pathway has their strong effects on most of proteins degradations and their formations of their new products forms of amino acids peptides which can be necessary for rebuilding MHC class-I subunits which will be directed to nucleated cells for endocytic MHC class-II productions. Estrogen formed from Ser/Thr mTOR Fox signaling pathways for glucocorticoids synthesis.

**Upon OPA1 enzymes effects on estrogen, but the feedback of GC to produce estrogen will upon ATPase & cox on GCs isoforms:**

Fatty acyl-CoA synthetase that can be used for re-activating glucocorticoid-gamma productions, while the effects of synthase on acyl-CoA-synthetase (gamma subunits) will produce glucocorticoid-beta which can produce IL-beta that can reactivate astrocyte, netrin-1, and neutrophiles functions.

The glucocorticoid Receptor (GRs) has roles of function of re-activating steroid hormone upon ATPase and cox via ser Thr Fox signaling pathways, and mitochondrial matrix repair and activations, throughout reactivate S6K1 synthesis for ribosomal ATPase and GTPase productions which necessary for OPA1 repair, where glucocorticoid (GC) contains the estrogen receptors that GR has strong roles for estrogen biosynthesis and vise versa in different pathways the first through ATPase Effects via Ser/Thr FOX pathways for re-producing estrogen, but second through OPA1 oxidative processes on estrogen, and strong roles in anti-inflammatory pathways.

The glucocorticoids (GCs) Biosynthesis pathways is linked to Estrogen biosynthesis and kinases protein that promote Estrogen synthesis, where GCs bio-synthesis is regulated by two imp keys 1st is the pro-nutrients-mTOR Ser/Thr-Fox signaling pathway for producing the four necessary types of kinases as described before, 2nd is the effects of OPA1 enzymes on the four kinases for producing fatty-acyl-CoA-synthetase, fatty-acyl-CoA-synthase, and fatty-acyl-CoA-phosholipase, where the latter is considered necessary for SIRPα1 production and then for TLR4 synthesis for the plasma membrane synthesis and for collagen synthesis.

The effects of synthetase on estrogen is the 1st steps for analyzing Estrogen for producing glucocorticoids-gamma subunits and utilizing active signals for activating followed processes which is glucocorticoids-beta upon dynthase effects on GC-gamma.

GC Gamma is the basic units for netrin-1 synthesis which is the basic for the neutrophile repairs and reactivations.
Glucocorticoid’s synthesis begins from estrogen upon effects of synthetase for GC gamma production, followed by beta-oxidation by the effects of synthase for producing glucocorticoids-beta and others Beta-subunits that can show enhancing and increasing in the uptake of other beta a myeloid protein [44] followed by phospholipase effects in case of proliferations processes through producing GC alpha.

Glucocorticoid-gamma has anti-inflammatory activities on inflammations for producing pro-inflammatory subunits due to the effects of acyl-CoA synthetase (gamma subunits) on inflammations for analysing their contents for starting anti-inflammatory pathways activity, and also GC-beta has the same anti-inflammation effect and has the function of SIRP synthesis from myeloid for the MHC class-I production which directed to nucleated cells to lie on and produce the endocytic MHC class II for the SIRPa production and for TLR4 synthesis.

GC- beta productions regulate GC-alpha which regulate membrane receptors through activating TLR4 started by SIRPa production. Brocken Estrogen by synthetase can activate a myeloid Beta-subunit synthesis.

Now the question is In case of diabetic disease is androgen can produce glucocorticoids and vise versa? In case of androgen synthesis due to deficiency in Ser amino acids lead deficiency in Ser /Thr-Fox signaling pathway will not produce GC gamma or GC beta upon ATPase Effects (depending on the % of Ser deficiency) but will produce GC alpha that also can produce SIRPa1 and TLR4 eith a deficiency in their pyrimidine nucleotides, but will not produce proper MHC class-I and also the MHC class II will not be produced in nucleated cells that diabetic patients will have a deficiency in T-cells re-activations and in macrophages reactivation.

Also, Androgen in diabetes disease can increase mainly the S6K1 resynthesis and ATPase productions and reactivities due to the Androgen is rich of purines and at the same time can increase not proper SIRPa and TLR4 for only reactivating ribosomes and OPA1 repairs with re-increasing in S6 synthesis.

Estrogen availabilities can reactivate OPA1 synthetase activities that can promote pyrimidines production for hydrphobic amino acids synthesis, while Androgen cannot promote and cannot activities synthetase functions that can’t activate hydrophobic acids synthesis, also has not the abilities to produce both proper GC gamma, beta and SIRP, consequently androgen cannot activate MHC class-I productions and Supress IFN gamma productions [45].
Conclusion:

S6K1 consider as protected basic subunits for Interferons (IFNs) isoforms synthesis regulated by pyrimidine-kinases.

Proper GTPase implicate cell migrations in case of availabilities of both PS/T-Cytosine kinases and PS/T-thymine Kinases (and in availability of proline and hydrophobic amino acids that accelerate OPA1 anabolic oxidative processes properly) that can increase Tyrosine metabolic pathways and will increase signals transmissions that will promote the migrations of active of genes and subunits which can activate beta-oxidative processes and alpha-oxidations (that regulated by synthase and by phospholipase respectively), that can promote phosphatidic acid (PA) to re-binds to mTOR and to re-binds to S6K peptides independently of mTOR-FOX pathways.

MHC class-I considered as fatty-acyl-CoA-synthetase (gamma-subunits) and considered as IFN-gamma that can analyze infected cells and inflammations then bind to their peptides for modify and promote IFN-beta synthesis upon synthase oxidations covering nucleated cells membranes for reproducing MHC class II which considered as fatty-acyl-CoA-beta (IFN-beta) that upon alpha-oxidations will promote fatty-acyl-CoA-phospholipase which considered IFN-alpha for regulating TLR4 synthesis upon the same alpha-oxidations for plasma membrane synthesis which contain MHC class II, and then again act on inflammations and on infected cells through feedback for re-producing IFN-beta then IFN-gamma regulated by OPA1 oxidations across cells membrane.

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The decreasing or deficiency in S6K1 productions will reflect the decreasing in the ATPase that will reflect decreasing in fatty acyl-CoAs production which done by OPA1 oxidative effects that will reflect

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decreasing in NAD and FAD that lead to the beginning of many diseases as asthma, diabetes, cancers... etc.

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SIRP-gamma (IFN-gamma ) productions are necessary for acting fast on inflammations and infection-ed cells for analyzing their contents then bind to resulted peptides for modifying its own sensor subunits and for promoting the productions of MHC class-I and SIRP-2-Beta (IFN-beta) upon regulations effects of OPA1 synthase enzyme which will directed to nucleated cells membranes to sit and lie on as MHC class-I which will promote the the endocytic soluble MHC class II which can considered as SIRP-Beta (IFN-beta) synthesis which upon alpha-oxidations by phospholipase effects will produce SIRPα (IFN-alpha ) which will be directed to promote TLR4 synthesis for modifying plasma membrane and for necessary proliferations, where through feedback the SIRPα1 and TLR4 will promote the irpregulations of MHC class-I through OPA1 enzymes on the external cells membranes for further acting on inflammations and reactivating synthetase enzyme-oxidations for acting on inflammation and for SIRP-gamma synthesis which can regenerate glucocorticoid-gamma and Estrogen re-synthesis.

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