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# Rac1 Rich Proline are OPA1 Flux Influencer for PLCs and IFNs Synthesis where Immune and Toxicity Due Deficiency in Synthetase and in Proline Synthesis

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ABSTRACT

Rac1 is basis for ATPase, ribosomes repairs, Gactin activities, and regulating fatty Acyl-COA productions (upon OPA1 function) which are main for epidermal growth factor "EGF" synthesis and for both PLCs and IFNs synthesis. Rac1 basically are S6K rich Proline and hydrophobic amino acids that each amino acid especially Proline characterize Rac1 for scpsific functions and activity for regulating specific anti-inflammatory cycles and specific anti-inflammatory growth, that Rac1 has the roles of acting on inflammatory sources for analyzing and producing long fatty chains which will follow the OPA1 oxidative function (which activated by GTPase which promoted by Rac1 active molecules ) for producing fatty Acyl-COAs isoforms which considered as GP-GTP isoforms Gp-GTP gamma, GP-GTP beta, and GP-GTP alpha isoforms where some said that GTPase has been analyzed to give Gp isoforms but GTPase has activated OPA1 enzymes which produced Gp-GTP nuclear isoforms upon effect on long fatty chains, that GP-GTP beta and alpha have the roles of promoting PLCs and IFNs isoforms for anti-inflammatory processes and for anti-inflammatory growth . That The Rho family Rac1-GTPase (Gp isoforms) mediates a variety of signal transduction processes leading to activation of NADPH oxidase, actin cytoskeleton reorganization and anti-inflammatory growth.

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The main active amino acids that most imp amino acid that Characterized the Rac1 function are the Proline amino acids and then hydrophobic amino acids (Tyr, Ser, Leu,), where Proline have basic oxidative roles in amino acids synthesis (regulated by aminotransferase). Also the synthesis of proline itself are carried out from conversion of glutamate to Proline, that the Deficiency in synthetase and in Proline synthesis due to decreasing in oxidative phosphorylation processes (regulated by OPA1 synthetase) will lead to accumulation of glutamate in brain and in neuronal tissues which is the sign of immune toxicity and signs of neuronal toxicity.

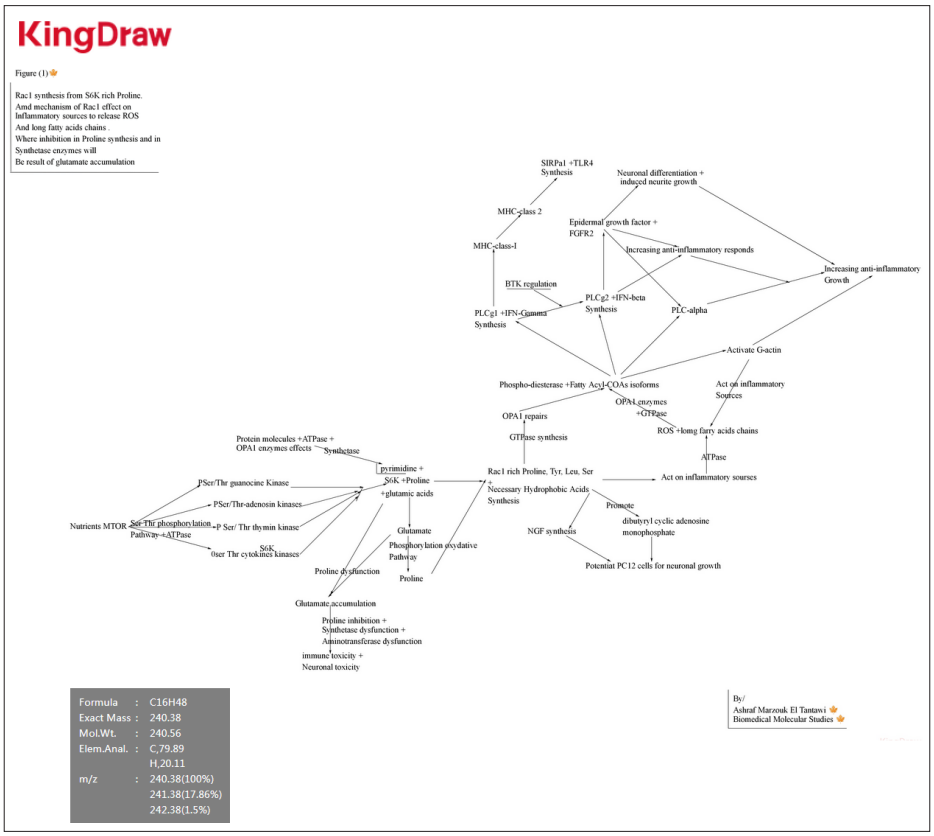
As Proline promote the amino acids synthesis by aminotransferase regulations, as the presence of Proline in Rac1 will perform the same roles of amino acids synthesis for DNA synthesis by repairing the deficiency of amino acids through rebinding with nucleotides during amino acids synthesis, and for thioesterase binding to form Rac1 thioesterase which will stimulate PLCγ1 then Plcγ2 for TXA2 synthesis for platelets renewing.

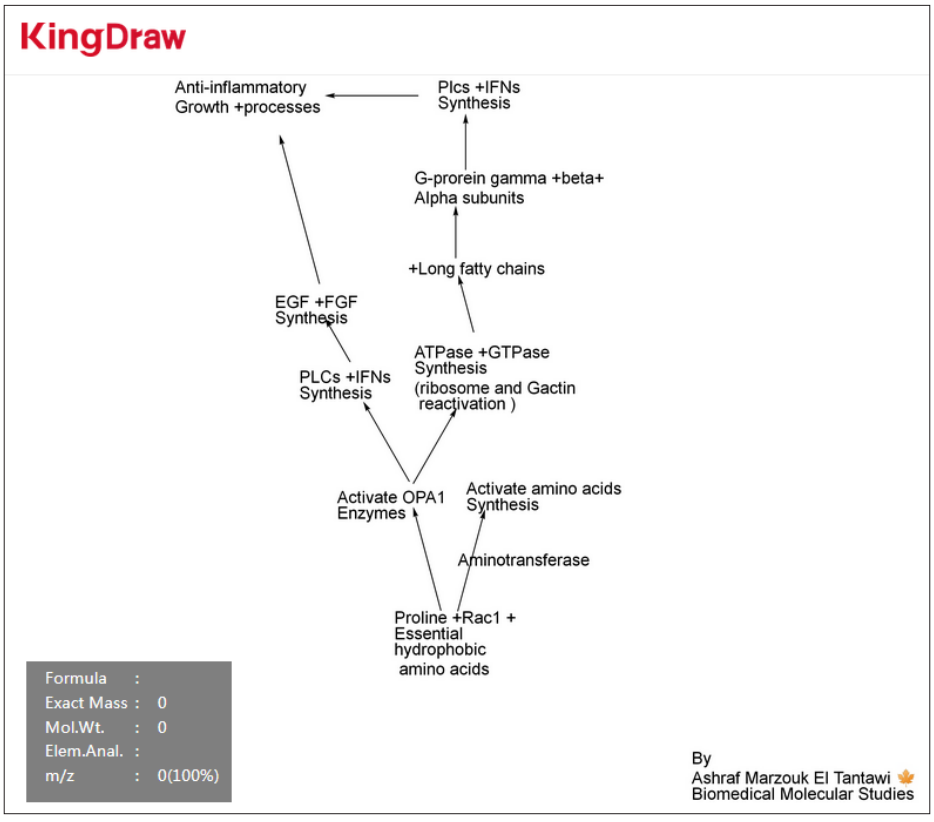
KPNA2 (which have the glutamatergic effect necessary for Proline synthesis from glutamate that prevents the accumulation of glutamate and protect the availability of Proline coverage and hydrophobic acids in Rac1 molecules for running various dependent cellular activities including anti-inflammatory growth. Vit D metabolites takes place in liver and in blood that bound to proteins then upon histone deacetylase and amino-transferase to promote Proline synthesis for active proper Rac1 synthesis. BCL-6 is regulated by Rac1-rich Proline Signaling activities, that Rac1 regulates and control genes transcriptions processes, and bind to protein for phosphorylation oxidative processes for activating Gp-GTP active subunits productions necessary for PLCs and IFNs productions which are necessary for anti-inflammatory cycles and for anti-inflammatory growth mediated by PLCγ2 and IFN-beta production. The Aminotransferase enzymes which activated by Proline in Rac1 are necessary for recovering the Hyperammonemia toxicity.

The activation of glutamate receptors and Rac1-GTP subunits receptors can activate and increase microtubule de polymerization due to conversion of glutamate to Proline synthesis and then due to promoting Gp GTP subunits upon activating OPA1 by GTPase molecules synthesis for acting on inflammatory long fatty chains which firstly formed due to effect of Rac1 on inflammatory sources (where Proline synthesis prevent glutamate accumulation and activate Rac1 synthesis regulated by OPA1 synthetase enzymes).

That firstly Rac1 molecules act on inflammatory sources for producing phorbol +ROS + long fatty chains productions which upon OPA1 effects will create the fatty Acyl-COAs "G-proreins-GTP isoforms" which promote and increases neuronal growth and immune anti-inflammatory upon PLCs and IFNs productions. So, it can be understandable that is why Rac1-rich-Proline (and Tyr, Ser, Leu) are so necessary for regulating various of cellular Biosynthesis, including anti-inflammatory growth, PLCs and IFNs synthesis, bones growth, DNA repair, binding to phosphorylation protein, TXA2 synthesis, and T-cells modulations too.

The necessity of proline synthesis (to prevent glutamate synthesis) for regulating amino acids synthesis regulated by GSA aminotransferase are so necessary to promote ALA synthesis in heme. The inhibition or Proline synthesis reflect Extracellular glutamate accumulation and inheritance in aminotransferase that will cause neurotoxicity and brain damage. Also, Inhibition in Pproline and consequently in proper Rac1 synthesis can cause hypoxia that will be main reason for decreasing the stimulation of OPA1 enzymes oxydative processes and decreasing in G-prorein-GTP-subunits synthesis. Also, Inhibition in Sestrins (gamma, beta, and alpha) genes in invertebrates reflect the accumulation in long fatty chains and increasing in oxidative damage, and mitochondrial OPA1 dysfunction that will be the result of inhibition in G-prorein-GTP-beta and G-prorein-GTP-alpha productions that followed by inhibition in PLCγ2 and in IFN-beta productions.



## Materials

- Rac1 active molecules
- Proline and hydrophobic amino acids
- Aminotransferase
- Mitochondrial OPA1 membrane
- ATPase and GTPase
- G-proreins isoforms Gp-gamma, Gp-beta, Gp-alpha
- Karyopherin alpha 2 "KPN-A2" (which have the glutamatergic)
- Vit D
- PLCs and IFNs synthesis regulated by fatty Acyl-COAs which regulated by Rac1 oxidative phosphorylation on inflammatory sources
- SESN2 synthesis basically regulated by active Rac1 and BTK in liver
- Leu synthesis regulated by Proline necessary for promote Leu-pentapeptides and Met- pentapeptides synthesis for enkephalin activities
- activating Cdc42 or Rac1-GTPase which is Rac1-GTP-beta necessary for promoting Plcγ2 and IFN-beta for anti-inflammatory processes
- Rac1-GTP-alpha necessary for PLC alpha and IFN-alpha necessary for anti-inflammatory growth
- BCL6
- Nerve growth factor "NGF" and epidermal growth factor "EGF"
- Aminotransferase is necessary for deleting the Hyper-ammonemia in vivo

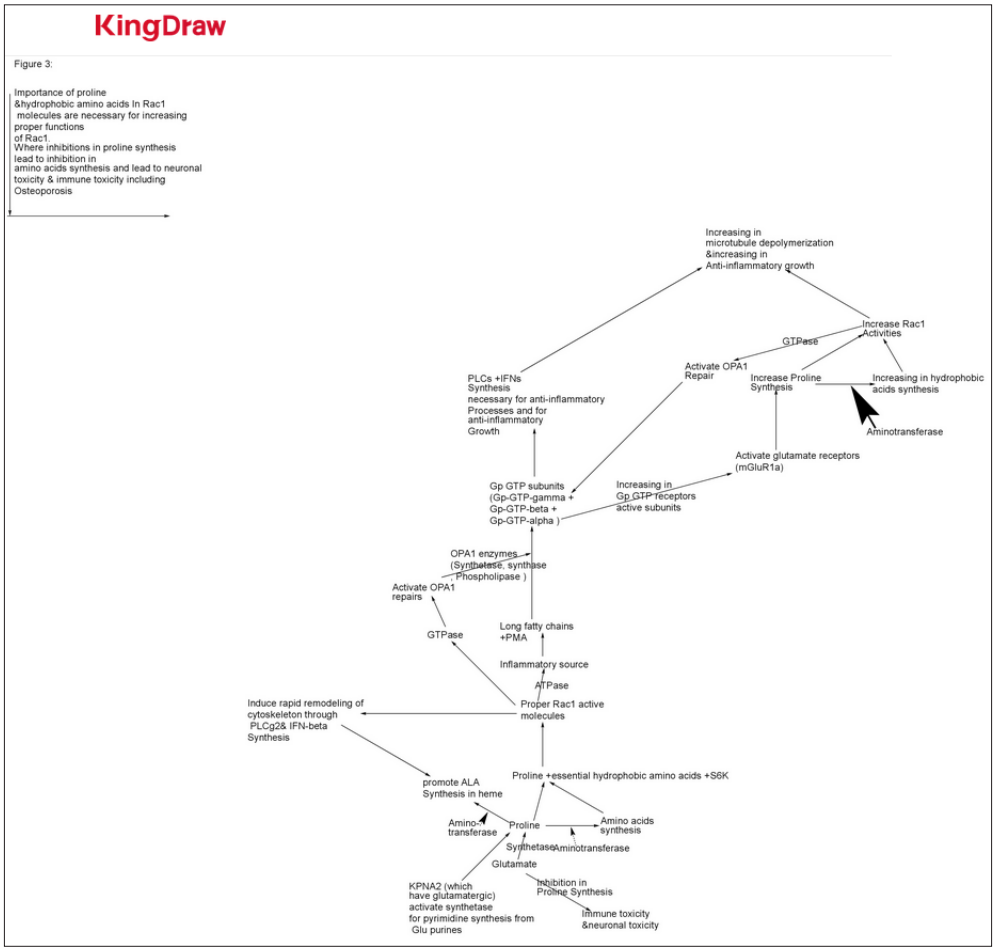
## Instructions

## Methods and Results

Rac1 is basis for ATPase, Gactin growth and for fatty Acyl-COA productions (upon OPA1 function) which are main for EGF synthesis and PLCs synthesis, where any deficiency in the main proper Rac1 synthesis will lead to mutated EGF synthesis that will lead to metastasis due to decreasing in the efficiency of Rac1 synthesis. Where, the interaction between PLC-γ1 SH3 domain and Rac1 play a significant role in EGF-induced F-actin formation and cell migration [1].

S6K containing enough Proline and hydrophobic amino acids (Tyr, Leu Ser, Pro...) which produced from mTOR Ser Thr phosphorylation will activate JAK signaling for SH3 productions are necessary for activating Acyl-COA gamma for PLCγ1 productions where both interaction will induce both Plcγ2 and epithelial growth factor (EGF) that will have imp. Roles in G-actin filaments growth and at the same time induce electron charges and signals migration for activating the rest of anti-inflammatory cycles and anti-inflammatory growth processes.

Proline is the only amino acid that the side chain is connected to the protein backbone twice, forming a five-membered nitrogen-containing ring, that is why Proline in Rac1 gives the advantages of amino acids synthesis, DNA repair, tissue growth that are so important for proliferation. Proline biosynthesis done through glutamate phosphorylation to γ-glutamyl phosphate by γ-glutamyl kinase, reduced to γ-glutamyl semialdehyde by γ-glutamyl phosphate reductase, cyclized spontaneously to Δ(1)-pyrroline-5-carboxylate and reduced to proline by Δ(1)-pyrroline-5-carboxylate reductase [2].



Where, Deficiency in Proline synthesis due to decreasing in oxidative phosphorylation process will lead to accumulation of glutamate in brain and neuronal tissues which is sign of immune toxicity. And also, as Proline promote the amino acids synthesis through necessary aminotransferase regulations, as the presence of Proline in Rac1 will perform the same roles of amino acids synthesis for DNA synthesis by repairing the deficiency of amino acids by rebinding with nucleotides during amino acids synthesis, for thioesterase binding to form Rac1 thioesterase which will stimulate PLCγ1 then Plcγ2 for TXA2 synthesis for platelets renewing.

That, Rac1 appears for protein kinase binding for stimulating fatty Acyl-COAs synthesis upon OPA1 enzymes activities for producing gamma, beta, and alpha Acyl-COAs for IFNs and PLCs for Gactin re-activities, for bone growth, anti-inflammations, for T-cells modulations and for cells proliferation. Also, as Rac1 has the roles of protein localization to plasma membrane and for inflammatory response (eg localization of MHCs on cells membrane for SIRPa1 and TLR4 syndrome (regulated by IFNs synthesis) as indicating Rac1 is the main basis for the various cellular processes eg for regulating PLCs and IFNs Biosynthesis, where Rac1 has roles of for designing and creating necessary proteins according to inflammations responds necessary for anti-inflammatory growth and necessary for creating MHCs and PLCs to be located on plasma membrane for activating anti-inflammatory cellular processes and growth.

Where, Rac1 promotes intestinal epithelial restitution by increasing Ca2+ influx through interaction with phospholipase C-1 after wounding. And, expression of activated versions of the Cdc42 or Rac1-GTPase restores antigen-stimulated Ca2+ mobilization necessary for degranulation in these mutant cells [3,4]. Rac1 are a specific S6K-rich-Proline molecules that are strong regulator and activator for PLCγ1 synthesis upon Rac1-GTP-gamma synthesis for restore Ca+. Rac1 activities start by both ATPase and GTPase productions, where GTPase necessary for activating mitochondrial OPA1 membrane for for activating OPA1 enzymes for creating designed necessary anti-inflammatory protein responds through BTK regulations and PLCγ1 synthesis will produce PLCγ2 synthesis for anti-inflammatory processes followed by PLC-alpha and IFN-alpha synthesis for anti-inflammatory growth including bone growth, epidermal growth and Ca restoration.

And, the Rac1 functions are controlling and regulate the representation of genes transcription. That, the transcriptional repressor BCL-6 is regulated by Rac1 Signaling activities. That Rac1 mediate repression of gene transcription [5].

Rac1 functions are controlling and regulate the representation of genes transcription. that has the roles of promoting amino acids synthesis upon is containing Proline which is so necessary for amino acids synthesis (regulated by aminotransferase)and has the oxidative function on inflammatory source for designing and re-creating the new designed protein chain firstly in the form of G-prorein gamma then G-prorein beta and then G-prorein alpha that are responsible for PLCs and IFNs synthesis for anti-inflammatory purposes and anti-inflammatory growth that includes B-cells maturation, T-cells modulations for anti-inflammatory responds, and includes TXA2 synthesis. Also, Rac1 functions has a significant influence on certain brain functions like neuronal migration, synaptic plasticity, and memory formation via regulation of actin dynamics in neurons [6].

Rac1 functions has a significant imp roles in activating both ATPase and GTPase productions where has imp roles of acting on inflammatory sources as wounds and suppurationsand generating ROS and long fatty acids chains that consequently will influence and promote OPA1 enzymes activities for producing Acyl-COAs isoforms necessary for PLCs and IFNs synthesis for increasing anti-inflammatory processes and growth that can influence on certain brain functions like neuronal migration, synaptic plasticity, and memory formation via regulation of actin dynamics in neurons activities and growth through reactivating G-actin for neuronal migration, synaptic plasticity, and restore memories which can be run by sestrins synthesis which can be started by signals migration from stimulated Rac1 activities, that SESNs synthesis are regulated by re-activating B-cells upon PLCγ1 and IFN gamma functions for promoteing PLCγ2 synthesis (upon BTK regulations) where SESNS are molecules needed for migrating amino acids and necessary for activating brain cells functions eg Leu and Met pentapeptides necessary molecules for enkephalin tissue activities which are necessary for activating memories and restore them in various tissues cells including brain. Bone morphogenetic protein 2 (BMP-2) consecutively and interdependently activates the wingless (Wnt)–β-catenin (βC) [7].

The Rho family Rac1-GTPase mediates a variety of signal transduction processes leading to activation of NADPH oxidase, actin cytoskeleton reorganization, transcription activation, and stimulation of DNA synthesis [8]. That as Rac1 contain active Proline which can form Rac1 GTPase upon stimulating GTPase synthesis for reactivating OPA1 enzymes activities that will include creating signals transmission necessary for stimulating OPA1 enzymes activities, as Rac1 is carrying the imp function for activating Gactin for neuronal growth and activities, and has the imp roles for controlling and adopting transcription processes that will include creating active signals for activating necessary enzymes proteins for amino acids synthesis, and for DNA synthesis commentaires eg Activating aminotransferase for amino acids synthesis and activating OPA1 enzymes for pyrimidine synthesis (upon synthetase effects) necessary for hydrophobic amino acids synthesis.

Since Proline needed for transferase enzymes for producing ornithine which necessary for amino acids synthesis as Rac1 regulate DNA synthesis, B-cells maturation through regulating PLCγ2 synthesis and regulate antigen synthesis. That originally Rac1 Biosynthesis regulated firstly by S6K productions from nutrient mTOR phosphorylation (regulated by ribosomal ATPase) pathway containing enough Proline and necessary hydrophobic amino acids necessary for Rac1 active functions including reactivating OPA1 enzymes through producing GTPase enzymes, that OPA1 enzymes necessary for producing Acyl-COAs upon acting on long fatty chains (which produced from the effects of Rac1 on inflammatory sources).

Where it has been reported that Rac1-dependent Protein Kinase N-γ Promotes Phospholipase Cγ1 Activation, Ca2+ Signaling, Rac1-dependent Protein Kinase N-γ (G-prorein kinases) are the basis of regulations for Promoting Phospholipase Cγ1 activities (through firstly activating Acyl-COAs synthesis by OPA1 effects) which then promote PLCγ2 and IFN beta (IFNγ2) synthesis which promote anti-inflammatory growth and create the new active anti-inflammatory subunits according to inflammatory responds.

The Rac Molecules when characterized with the availability of the active Proline which contain active oxygen linkages will have the ability to run oxidative analyzed processes to act on fatty nutrients Molecules and inflammatory molecules for producing long fatty chains, and in the main time will stimulate synthetase enzymes

within OPA1 membrane for acting n inflammatory source for producing phorbol esters and long fatty chain and running the pyrimidine synthesis from purines that pyrimidine will be the mediator in the necessary Hydrophobic amino acids synthesis (which regulated by aminotransferase enzymes) especially Tyr, Ser, leu, Met and ÎLe which will activate tyrosine phosphorylation cycles and BTK which are so imp for activate PLCγ2 ( from PLCγ1) that PLCγ2 will activate B-cell maturations, anti-inflammatpry processes and anti-inflammatory growth through activating PLC-alpha by more phospholipase that will activate the functioning Ca+ to be migrated to the under configurated tissue.

As, S6K containing enough Proline and necessary hydrophonic amino acids (as Tyr, Ser, Leu.) which are the basis of Rac1 and having roles of -4,5-bisphosphate 3-kinase activity, ATPase binding, GTPase production and binding and nucleotides binding , as indicating Rac1 have the roles of activating ATPase through ribosomes repair and promote GTPase re-production (which necessary for OPA1 repair), that Rac1 necessary for activating ATPase (whether in ribosomes or in Gactin filaments) for acting on lipids molecules (fatty inflammatory sources) for producing long fatty acids chains which upon OPA1 enzymes effects will produce fatty Acyl-COA-gamma, beta, and alpha respectively which regulate PLCs and IFNs synthesis [9].

And also Rac1-rich Proline have the roles of nucleotide binding through amino acids synthesis for analyzing the proteins (faty chain) for producing nucleotides molecules for producing ornithine (upon aminotransferase effects) upon availability of Proline in Rac1, so Rac1 has the role of amino acids synthesis. So now it can be understandable that why Rac1 rich Proline (and Tyr, Ser, Leu) are so necessary in regulating various of cellular Biosynthesis, including bones growth and immune effective growth, and T-cells modulations too.

Rac1 can modulate OPA1 repairs for nuclear Rac1 which mediated by Acyl-COAs synthesis for nuclear Rac1 GTPase synthesis that will be accumulate on nucleus for bFGF productions necessary for neuronal differentiation and growth, and neurite outgrowth which induced neuronal differentiation in PC12 cells. Where, Rac1 translocation to the nucleus functionally correlates with bFGF-induced neurite outgrowth [10].

Notice that Karyopherin alpha 2 (KPNA2) (which have the glutamatergic synapse and has histone deacetylase binding functions mediates the nuclear import of Rac1 by directly binding the NLS through active GTP-bound Rac1 nuclear compartment during Cell differentiation-related role for nuclear Rac1. That KPNA2 (which have the glutamatergic effect necessary for Proline synthesis from glutamate that prevents the accumulation of glutamate and protect the Pproline coverage and hydrophobic acids in Rac1 for running various dependent cellular activities.

Vit D metabolites takes place in liver and in blood that bound to proteins then upon histone deacetylase and amino-transferase will promote Proline synthesis which will be directed for necessary Hydrophobic amino acids synthesis upon aminotransferase effect (and mediated by synthetase functions for pyrimidine synthesis) for proper amino acids synthesis, that previous pathway can be promoted by vitamin D which promote own vit D receptor (VDR) Upon stimulating and activating OPA1 enzymes effects for active proper Rac1 synthesis from histone deacetylation and from glutamate for controlling and regulating various transcription and cellular processes. where VDR is a transcription factor that partners with other transcription factors such as retinoid X receptor when bound to 1,25(OH)2D regulates gene transcription either positively or negatively depending on other cofactors to which it binds or interacts [11].

Notice that Rac1 has a role of biological processes of vascular endothelial growth factor receptor that indicate Rac1 has the main regulations for endothelial growth that has the main control for building main receptors for endothelial growth mediated by PLCγ2 and IFN-beta synthesis for improving anti-inflammatory cycles followed by PLC-alpha and IFN-alpha systems for anti-inflammatory growth mediated by SIRPa1 and TLR4 synthesis.

Neuronal migration and axon growth are basically promoted and regulated by availability of active Proline in Rac1 molecules which regulate signals migration and G-actin activities (upon GTPase production) in a pathway mediated by GTPase synthesis for promoting OPA1 enzymes influencer fluxes for acting on long fatty acids chains (which produced upon Rac1 effect on inflammatory sources) for fatty Acyl-COAs synthesis started by Acyl-CoA-Gamma, followed by acyl-CoA-beta then by Acyl-CoA-alpha "for PLCs and IFNs synthesis, where Rac1 rich Proline are key events for neuronal developments, and the main regulator needed for improvements in the cytoskeleton started by anti-inflammatory improvements followed by anti-inflammatory tissue growth. That Rac1 recruits the WAVE complex to the plasma membrane to enable actin remodeling necessary for axon growth [12].

The remodeling actin is proceeded upon Rac1 functions through promoting GTPase synthesis (upon the type of received signals) that will be able to promote OPA1 repair which will promote the G-prorein GTP subunits synthesis which are so imp for PLCs and IFNs synthesis for activating G-actin re-modulations for axon growth.

Rac1 promote GTPase synthesis (upon the type of received signals) that will be able to modulate actin remodeling which necessary for axon growth. Rac1 will activate several pathways necessary for remodeling neurons upon anti-inflammatory responds and growth eg promoting fatty acids chains synthesis then produce GTPase for activating OPA1 for activating PLCs and IFNs isoforms synthesis for beta-cells maturations, T-cells modulations and TXA2 synthesis for feeding new cells and tissues.

The presence of 1α,25-Dihydroxy-Vitamin D3 (1α,25(OH)2D3) in tissue (which produced upon hydroxylase effects on Vit D) will increase the OH linkages function that can increase the oxidative binding activity for Rac1 rich Proline synthesis through increasing the Proline synthesis that will consume glutamic and glutamate found in vivo then recreate modified active Rac1 molecules through availability of their active Proline and active hydrophobic amino acids that can increase the Rac1 oxidative function on producing long fatty chains + ROS (upon Rac1 and ATPase effects on fat and on inflammatory sources) and then will promote GTPase for promoting OPA1 enzymes activities (OPA1 repairs) for producing fatty-Acyl-COAs isoforms (G-prorein GTP subunits) which necessary for activating both PLCs and IFNs for modulating anti-inflammatory processes and growth including B-cell maturations.Where,1α,25-Dihydroxy-Vitamin D3 (1α,25(OH)2D3 can modifies actin cytoskeleton in Ishikawa cells, a well differentiated endometrial carcinoma cells line [13]. Also, Rac1 are activating the amino-transferase enzymes for amino acids and Proline synthesis necessary for creating subunits for anti-inflammatory growth and cells proliferation if likely an be potentiated by presence of vit D 3 (1α,25(OH)2D3) which formed in vivo upon hydroxylase effects on Vit D. The main

activities of Rac1 (that considered as active S6K rich Proline) is re-activating both ATPase and GTPase productions, where GTPase are necessary for OPA1 repair for their enzymes fluxes functions for Acyl-COAs isoforms productions which necessary for PLCs and IFNs synthesis which are necessary for cellular growth and anti-inflammatory growth too. That PC12 cells is potentiated by dibutyryl cyclic adenosine monophosphate (dbcAMP) which is the property for nerve growth factor "NGF" too. mediated by G-prorein GTP subunits productions and PLCγ1 with IFN-Gamma synthesis for nerve growth factors synthesis. That both NGF and bFGF may share common intracellular events leading to neurite outgrowth and synergism with dbcAMP and forskolin [14]. The G-prorein beta subunits is produced upon hydrolysis of Rac1-GTPase molecules by synthase oxidative effects which preceded by effect of synthetase oxidative process on Rac1-GTPase for producing G-prorein gamma "Gpγ" which promote fatty Acyl-COA beta "GpB" synthesis. Where, Gβγ in PC12 cells induced neurite outgrowth but in the absence of added NGF. That glutamate receptors in vivo which I consider it as long fatty chains as analyzed protein upon ATPase and Rac1 effects that can be remodulated by OPA1 enzymes effects for fatty Acyl-COAs which promote NGF and FGFR2 synthesis for activating Gactin and microtubule depolymerization.

Where it has been reported that Activation by Gq-coupled muscarinic receptors or glutamate receptors (mGluR1α) causes microtubule depolymerization and association of tubulin with plasma membrane proteins in living cells [15]. Notice, activation of glutamate receptor by OPA1 enzymes will promote pyrimidine synthesis and Proline synthesis which promote, then will activate hydrophobic acids synthesis which will promote the proper G-prorein– GTP subunits receptors synthesis which will activate PLCγ2 and IFN-beta synthesis that will activate the increasing of microtubule de polymerization due to conversion of glutamate to Proline upon OPA1 effects and increases neuronal growth and immune anti-inflammatory growth.

The active G-prorein alpha "Gα" subunit 12/13 regulates small GTPases affecting the actin and tubulin cytoskeleton. Gβγ subunits may also activate effector molecules, such as ion channels [16]. Studies suggest that α and βγ subunits of G proteins interact with tubulin/microtubules to regulate assembly/dynamics of microtubules, providing a novel mechanism for hormone or neurotransmitter induced rapid remodeling of cytoskeleton [17]. But, actually I report that Gp-α and Gp-βγ subunits of oxidized G-proteins by synthase & by phospholipase regulate various cellular activities including MHC-class-I and MHC class 2 then SIRPα1 and TLR4 for anti-inflammatory growth and proliferation, that those Gp-Beta and Gp-alpha promote anti-inflammatory growth and providing a novel mechanism for neurotransmitter induced rapid remodeling of cytoskeleton.

That , actually I report that Gp-α, Gp-β, and γ subunits of oxidized G-proteins by GTPase, synthase & by phospholipase are originally formed due to the proper Molecular composition and activity of Rac1 that regulate various cellular oxidative activities including G-prorein GTP subunits synthesis which necessary for PLCs and IFNs productions and then for MHC-class-I and MHC class 2 then SIRPα1 and TLR4 synthesis for anti-inflammatory processes and growth and, that those Gp-Beta and Gp-alpha promote PLCγ1, PLCγ2, PLC-alpha, and IFN-beta and alpha for anti-inflammatory growth and providing a novel mechanism for neurotransmitter induced rapid remodeling of cytoskeleton.

My notes is, Active Rac1 is the S6K rich Proline and necessary Hydrophobic amino acids as Ser, Tyr, and Leu, that when Rac1 activated will have the functions of producing ATPase that can act on inflammatory source producing long fatty acids chains then at the main time will activate GTPase synthesis which activate OPA1 inner membrane for start producing their enzymes started by synthetase which has necessary roles for pyrimidine synthesis necessary for amino acids synthesis (regulated by Proline and amino transferase) and that enzyme necessary for acting on fatty acids chains for producing fatty Acyl-COA gamma mediated by dissociation of GTPase to bind with the Acyl-COAs gamma subunits that will be considered as G-prorein gamma (Gpγ), and then will follow the synthase effect on Gpγ to produce G-prorein-beta "GpB" which upon phospholipase effects will produce Gp-alpha which responsible for proliferation and anti-inflammatory growth, where that Previous pathway is done by activating phosphodiesterases necessary for Acyl-COAs isoforms which each isoform contain analyzed cleaved Gp from analyzed cleaved GTPase, and also that prevents Rac1 pathway is a necessary mechanism done through activating active Rac1 rich Proline and hydrophobic acids where that pathway is connected with the effects of Rac1 on inflammatory source for long fatty chains productions for stimulating the activated OPA1 (upon GTPase effect) to act on previous long fatty chains for producing the three G-prorein subunits isoforms where each has own step and functions for activating the second one GpB subunits which is necessary for activating and strengthen anti-inflammatory processes for activating the third G-prorein alpha subunits which responsible for anti-inflammatory growth activities.

As the last GpB and Gpalpha formed as will activate Polymerization of microtubules and regulate assembly/dynamics of microtubules, providing a novel mechanism for neurotransmitter induced rapid remodeling of cytoskeleton growth through activating PLCγ1 & Plcγ2 Synthesis for anti-inflammatory growth including the followed TXA2 synthesis (which regulated by PLCγ2 and BTK) .Where, the three G-prorein subunits isoforms are having their own active receptors which formed due to OPA1 phosphorylations pathway which produce Gpγ, GpB, and Gpalpha upon synthetase, followed by synthase then followed by phospholipase respectively.

Notice that, Gβγ interaction with tubulin down-regulates this signaling pathway. Purified Gβγ, alone or with phosphatidylinositol 4,5-bisphosphate (PIP2), inhibited carbachol-evoked membrane recruitment of tubulin and Gαq transactivation by tubulin (which is the 1st step regulated by synthetase for Gpγ synthesis), but Polymerization of microtubules elicited by Gβγ (which is GpB) that can reduce the inhibition of PLCβ1 (through activating the PLCγ2 synthesis) observed at high tubulin concentration. That study revealed the spatiotemporal pattern of Gβγ/tubulin interaction during carbachol stimulation of neuroblastoma SK-N-SH cells [18,19].

As I mentioned previously that Rac1 is a S6K-rich Proline as Rac1 ribosomal ATPase and regulate neurite growth through producing AMP potentiates bFGF-induced neurite outgrowth in PC12 cells through activating OPA1 enzymes which regulate the G-prorein gamma, beta, and alpha productions that activate anti-inflammatory processes growth. Where, AMP is the primary results from Rac1 through activating the releasing of ATPase for ribosomes and Gactin repair. That as Rac1 is S6K rich Proline (that can act as "T-RNA) that can activate ribosomes and Gactin filaments through releasing ATPase and GTPase synthesis, as Rac1 activate both ATPase and GTPase which activate and correlate the activation of long fatty acids chains through its effect on anti-

inflammatory source then will be followed by OPA1 enzymes activities for producing Acyl-COAs isoforms (gamma, beta, and alpha) which involve analyzing and oxidating Rac1-GTPase for producing the three subunits Gp-Gamma, Gp-beta Gp-alpha upon OPA1 enzymes oxydative processes which necessary for rebuilding neuronal growth and activate both PLCs and IFNs productions necessary for anti-inflammatory growth, where Rac1 and both PLCs and IFNs are necessary for sestrins synthesis but with availability of Proline, Tyr, Leu, Ser in the main Rac1 molecules (that will be described later).

Proper Rac1 rich Proline and necessary hydrophobic acids can be directed to ribosomes for repair and ATPase productions and then for promoting GTPase production where GTPase can bind to Rac 1 as a Rac1-GTPase to stimulate β-catenin-dependent transcription of Wnt target genes [20].

The effect of Rac1 on inflammatory source will produce ROS and phorbol ester (long fatty chains) upon the effect of ATPase, while GTPase will be released for activating mitochondrial OPA1 enzymes that will act on phorbol ester and long fatty chains for producing first the long fatty-acyl-CoA-synthetase "G-prorein-Gamma" active subunits with pyrimidines synthesis (upon synthetase effects) followed by G-prorein-Beta "GP-GTP-Beta" synthesis upon synthase effect then followed by G-prorein-GTP-alpha productions upon phospholipase effects on GP-G5P Beta, that fatty Acyl-COA-beta synthesis are so necessary for activating both PLCs, and IFNs isoforms synthesis then for Gactin functions , and for TXA2 synthesis upon Plcγ2 and BTK regulations.

PLC-gamma-1 (PLCγ1) promoted by Acyl-COA-gamma production upon effect of OPA1-synthetase on long fatty chains (which produced from effect of Rac1 on inflammatory sources) for producing Gp-GTP-gamma necessary for PLCγ1 productions and vice versa (upon synthetase activity then will produce Acyl-COA-synthase "upon synthase effect ", where PLCγ1 necessary for PLC-beta and PLC-alpha (upon effect of synthase and phospholipase respectively) for nerve growth factor "NGF" synthesis, then for IFN-beta and IFN-alpha synthesis which are necessary for B-cell maturations and activating BTK and sestrin synthesis, where availability of Leu amino acids in specific percentage in Rac1 are so necessary for activating SESN2 synthesis and for activating BTK for B-cell maturations and for SESN2 synthesis, that SESN2 necessary for reactivating brain enkephalin tissue and immune functions through activating Leu and Met-pentapeptides for activating Enkephalin tissue for activating brain and for restore memories.

PKC activators, PMA or bryostatin 1 (bryostatin) stimulates the growth of long neurites. PMA or bryostatin incubation followed by NGF activates PKC isoforms delta-, and epsilon-leading to outgrowth of long neuritis [21]. That the activations of long fatty acids chains synthesis (upon ATPase Effects and presence of Proline in Rac1) on inflammatory sources then followed by GTPase for activating OPA1 synthase oxidations for activating Acyl-COA beta (G-prorein-GTP) synthesis which followed the effects of phospholipase for NGF, for FGF and for Gp-alpha synthesis necessary for anti-inflammatory growth and for long neurites growth. That Rac1-GTPase ¬> Gp three subunits upon OPA1 enzymes oxidative processes ¬>imp for G-actin repair and necessary for the growth of long neurites.

Neurons (nerve cells) can be considered also as fundamental units of the brain activities and nervous system, (that the activating nerve cells regulated by Rac1 and mediated by Gp GTP subunits production which necessary for PLCγ2 and IFN beta synthesis for NGF synthesis that necessary for SESN2 synthesis mediated by β-catenin) where Leu and Met pentapeptides are so important for enkephalin activities for brain cells function responsible for receiving and creating new responds signals for active G-prorein subunits motors commands for modulating anti-inflammatory responds and for restore memories. The Pathway of Proline synthesis from glutamate are so important for amino acids synthesis (regulated by aminotransferase and synthetase) and are necessary to be involved in Rac1 molecules for strengthen activity of Rac1 for easier acting on inflammatory source with ATPase for producing long fatty chains which upon the OPA1 effects will produce G-prorein-GTP-subunits which will increase PLCs and IFNs synthesis necessary for increasing anti-inflammatory processes and growth.

Where, Extracellular glutamate secretion into brain tissue causes neurotoxicity and brain damage [22]. That neurotoxicity and brain damage are due to deficiency in proline synthesis that can reflect deficiency in aminotransferase enzyme activities that can reflect deficiency in amino acids synthesis and accumulation in glutamate in brain, that the accumulation of glutamate not because are upon extracellular secretion but the glutamate accumulation due to inhibition in Proline synthesis and inhibition in aminotransferase activities.

My note is the Neuroprotective activity of oxytocin (OT) in ischemia of various tissues has the function of the ability of improving amino acids synthesis that due to improving in aminotransferase enzymes activities lead to improving in Proline synthesis (lead to decreasing in the accumulated glutamate) that will lead to increasing in proper Rac1 synthesis which will act on inflammatory source for producing long fatty chains and ROS and in the main time Rac1 will activate GTPase production for activating OPA1 enzymes which will act on the primary long fatty chains fir producing the three G-prorein-GTP subunits (fatty Acyl-COAs) isoforms which will activate PLCs and IFNs productions which consequently will activate liver function for activating BTK and SESN2 synthesis.

Notice that SESN2 has the function of feeding and reactivating enkephalin brain tissue again through promoting Leu and Met pentapeptides synthesis which are necessary for enkephalin activities. That The inhibition of pyrimidine synthesis regulated by availability of synthetase, and deficiency in Proline synthesis will lead to accumulation of glutamate in brain which can reflect deficiency in aminotransferase enzymes. Notice, the activating of proper aminotransferase enzymes with availability of Proline and hydrophobic acids synthesis will activate the proper of Rac1 production and running its own roles of activities that can prevent glutamate accumulation and can reactivate Rac1 func for increasing the anti-inflammatory activity and anti-inflammatory growth and at the same time will increase liver function (mediated by NGF and by β-Catenin synthesis) for adopting the SESN2 synthesis for functioning fatty acids metabolism and reactivating brain and neuronal activity.

Where, as there are inhibition in Proline synthesis and in aminotransferase enzyme as will reflect accumulation of glutamate and deficiency in amino acids synthesis and will be the result of decreasing in proper Rac1 Biosynthesis which characterized by the presence of Proline and necessary hydrophobic acids as Tyr, Ser, and Leu, (that Leu necessary for SESN2 synthesis and for Leu pentapeptides synthesis), where the deficiency in proline will improve the deficiency in cartilage synthesis and deficiency in

amino acids Biosynthesis too (where, Proline are main regulator for amino acid synthesis upon amino-transferase function).

And also, Deficiency in Proline nucléotides triplets "ACC" will lead to accumulation of tryptophan "TGG" that will be result of increasing in Glu synthesis ((GAA - Glu <¬>CTT Leu GAG - Glu <¬> CTC leu)), but deficiency in synthetase functions will be result of decreasing in pyrimidine synthesis that will be the result of accumulation of purines in the form of amino acids as glutamate that will increase the accumulation of Glu synthesis "due to accumulation of purines". Neuronal cytotoxic can reflect accumulation of glutamate due to deficiency in synthetase functions and also reflect unavailability of Proline in Rac1 molecules (which necessary for synthetase activities) which can lead to inhibition in proper Rac1 activities, and will inhibit the stimulations of OPA1 enzymes activities that can reflect decreasing in the G-prorein-GTP productions (necessary for PLCs and IFNs synthesis) that will reflect decreasing in BTK and in SESN2 synthesis that will lead to accumulation of purines in the forms of "AGG" which is the increasing in Glu in brain (GAA, GAG Glu) with inhibition or decreasing in the Leu amino acids, where Leu active amino acids are necessary for SESN2 synthesis and activities.

Both Asp & Glu are carrying imp roles for activating and promoting the Leu and Met pentapeptides in enkephalin tissue that the deficiency or inhibition in Proline and in synthetase will inhibit Asp synthesis but not Glu (which consists of only accumulated purines) that will be the result of decreasing or inhibition in SESN2 synthesis and will be the result of accumulation of Glu and purines in brain with inhibition in Leu and Met pentapeptides synthesis lead to decreasing in enkephalin functions that will be result of immune toxicity and neuronal toxicity.

So immune toxicity characterized by decreasing or inhibition in synthetase with unavailability of proline amino acids (where synthetase has the roles of pyrimidines synthesis for hydrophobic amino acids synthesis then will need aminotransferase for the amino acids synthesis) that will lead to accumulations of purines in the form of Glu amino acids in brain with decreasing or inhibition in pyrimidine synthesis in liver and in brain too.

Notice that Asp with triplets "GAT - GAC" connected to Met for Met pentapeptides synthesis, But, Glu "GAA, GAG" are translated and connected with Leu (CTC) for Leu pentapeptides synthesis in brain, that when Proline and Leu inhibited will lead to accumulation of glutamate in brain.

Also, the Hepatic Encephalopathy and Hyperammonemia Produce Neuronal Communication Dysfunction due to inhibition in amino transferase activities and unavailability of Proline which can carry the function of improving Hyperammonemia Produce Neuronal Communication through running active amino acids synthesis and through improving SESN2 synthesis that will increase memories functions too. That hyperammonemia and hepatic failure induce alterations in glutamatergic neurotransmission [23].

The Hyperammonemia is mainly due to deficiency in Proline amino acids followed by deficiency in aminotransferase enzymes which reflects dysfunction in OPA1 stimulations that can increase the dysfunction in the long fatty Acyl-COAs synthesis that will be result of decreasing in the condensation of Acyl-COAs for SESN2 synthesis that will reflect decreasing in Leu amino acids synthesis and decreasing in Leu pentapeptides which necessary in enkephalin tissue in brain that will lead to dysfunction in neuro-transmission, decreasing in memories function , and in Neuronal Communication , that can reflect liver failure (failure in BTK and in PLCγ2) with accumulation in Glu in brain.

So, Deficiency in Pproline and in hydrophobic acids synthesis (with failure in synthetase functions) specifically in Tyr Leu, and in Ser that will reflect dysfunction in OPA1 activities that will be the result of decreasing in Acyl-COAs synthesis then in SESNs synthesis that reflects neuronal cytotoxicity with accumulation of glutamate "purines" amino acids. So, the deficiency in the ornithine-δ-aminotransferase (important in the synthesis of amino acids, including Proline and Leu ) are the signs of Deficiency in Pproline synthesis from glutamate that the sign of immune toxicity and neuronal toxicity with accumulations of glutamate , and result of deficiency in sestrins-Leu Biosynthesis and lead to neuronal cytotoxic [24].

That previous study indicate the imp roles of ornithine-δ-amino-transferase for Leu, Ser and Tyr synthesis where, the absence of that enzyme ornithine-δ-A-Trase will cause Glu accumulation and Hyperammonemia with dysfunction in neurotransmission in vivo that can lead to neuronal toxicity. Accordingly, inactivation of Sestrins (gamma, beta, and alpha) genes in invertebrates resulted in diverse metabolic pathologies, including oxidative damage, fat accumulation, mitochondrial dysfunction [25].

Because activation of SESNs synthesis requires activating OPA1 enzymes for Acyl-COAs, where activating OPA1 are running by Rac1 rich-Proline, where unavailability of Proline will be result of Deficiency or decreasing in OPA1 repair, decreasing in hydrophobic acids synthesis and decreasing in cartilage synthesis followed by decreasing in PLCs synthesis. That dysfunction in SESNs Biosynthesis will reflect dysfunction neuronal communication and transmission with Encephalopathy and Hyperammonemia due to mainly reductions in Rac1 rich Proline, and in aminotransferase enzymes that result of Deficiency in amino acids synthesis.

Notice, ornithine- aminotransferase "OAT" that regulated by ribosomes so by Rac1 as well, and is essential in creating ornithine from the Proline substrate for amino acids synthesis, so Proline is so necessary regulator as substrate for the synthesis of ornithine which is so necessary for hydrophobic amino acids synthesis that OAT gene is necessary for recover the Hyper-ammonemia through creating necessary Tyr, Ser, Leu hydrophobic amino acids for Rac1 synthesis, for OPA1 activities, for nuclear isoforms synthesis and for SESNs synthesis started by SESN-gamma "SESN1", then beta "SESN2", then alpha "SESN3" regulated by OPA1 synthetase, synthase, then phospholipase respectively.

So The immune toxicity defined as a dysfunction in both synthetase enzymes and in availability of Proline synthesis , where synthetase necessary for pyrimidine synthesis needed for amino acids synthesis, while Proline synthesis from glutamate are necessary for amino acids synthesis (regulated by aminotransferase), that deficiency in synthetase will be the result of accumulating purines in the form of Glu but deficiency in proline will result for deficiency in amino acids synthesis that will be the result of the deficiency in OPA1 function and dysfunction in amino transferase activities which reflects Hyperammonemia in vivo.

Also immune toxicity characterized by inhibition in kynurenine pathway and in tryptophan "TGG" (due to inhibition in synthetase activity) which is essential amino acid used for building protein , also immune toxicity characterized by inhibition in PLCγ1

and PLCγ2 where both regulated by OPA1 enzymes effects that consequently will reflect Inhibition in TXA2 synthesis (which regulated by PLCγ2 functions). Inhibition in thymine pyrimidine synthesis will be result in the inhibition in tryptophan TGG that will be result of accumulation in Thr amino acids ACC "purines" in blood and will inhibit Proline ACC synthesis (where, Proline synthesis is connected to the availability of tryptophan TGG in vivo.

Sestrin has necessary roles connected with Leu amino acid synthesis (which considered previously as regulated by Proline and then by aminotransferase) for running and functioning metabolic process for preventing reverse reactions, where absence of ornithine-δ-aminotransferase enzymes can lead to dysfunction in hydrophobic amino acids and Proline synthesis and consequently will reflect dysfunction in OPA1 stimulation and activities ,that lead to pathogenic Encephalopathy and Hyperammonemia in vivo and dysfunction in neuronal Communication and transportation. The dysfunction in pyrimidine synthesis regulated by synthetase lead to accumulations of purines in the form of Glu amino acids in brain and deficiency in synthetase can lead to deficiency in proline that will lead to deficiency in Ornithine synthesis (regulated by amino transferase enzymes) which formed from Proline lead to deficiency in hydrophobic amino acids synthesis, that lead to deficiency in Tyr, Ser including Leu (CTC "Leu"&TTC "Leu") that will reflect dysfunction in SESN2 synthesis and will be result of accumulation in Glu ("GAG" & GAA "Glu") that will be result of dysfunction in neuronal Communication (and transportation) and pathogenic Encephalopathy.

Factors NRF2 and NF-κB are coordinated effectors of the Rho family, GTP-binding protein RAC1 during inflammation, that RAC1 induces NRF2 signaling pathway [26]. That, nuclear transcription factor "NTF" are basically formed due to the effects of Rac1 on inflammatory sources by producing ATPase and GTPase for analysis inflammations for producing long fatty chains that will produce nuclear fatty Acyl-COAs isoforms upon the effects of OPA1 (which activated by GTPase) that will be followed BY NTF synthesis and then will stimulate PLCs and IFNs synthesis for running anti-inflammatory responds and anti-inflammatory growth. Remember that S6K rich Proline are the basis for Rac1 Which are necessary for activating OPA1 synthetase and other OPA1 enzymes for producing fatty Acyl-COAs "nuclear transcription factors" which coordinate analysis the inflammation molecules for finally increasing anti-inflammatory processes and growth including TXA2 synthesis regulated by PLCγ2 and BTK .

Where, negative Rac1 inhibits the development of NK cell–mediated cytotoxicity by two mechanisms. There is a rapid increase in Vav tyrosine phosphorylation during the development of antibody-dependent cellular cytotoxicity and natural killing [27]. Indicating that OPA1 oxidative phosphorylation are basis for development of antibody-dependent cellular cytotoxic For fast running FOX regulated by OPA1 for fatty Acyl-COAs isoforms (the three G-prorein subunits Gp-gamma, Gp-beta, and Gp-alpha ) for running their own pathways for producing proper PLCs and IFNs for running proper anti-inflammatory activities and anti-inflammatory growth for better cellular development.

GSA aminotransferase are necessary to promote ALA synthesis in heme Biosynthesis, that the net transfer of the amino group from the 2-carbon to the 1-carbon position to form ALA [28]. So it indicate the necessity of proline synthesis (to prevent glutamate synthesis) for regulating amino acids synthesis regulated by GSA aminotransferase which are so necessary to promote AL synthesis in heme. The first and rate-limiting step of heme Biosynthesis pathway is the condensation of glycine and succinyl-CoA to form 5-aminolevulinic acid (ALA), a 5-carbon aminoketone, in the mitochondria [29].

Where, it's important to know that the condensation of glycine and succinyl-CoA to form 5-aminolevulinic acid (ALA), a 5-carbon amino ketone are so necessary for SESN2 synthesis in availability of Leu hydrophobic acids by liver.

**Questions**

Is Ser inhibition signs for RORs inhibition and neuronal toxicity through leading to glutamate? And, is the inhibition in GTPase synthesis which regulated by S6K-rich Proline can inhibit OPA1 activities and can lead to neuronal toxicity?? Inhibition in Ser phosphorylation are sign for only accumulation of purines kinases (due to inhibition in pyrimidine synthesis and in amino acids synthesis ), where inhibiting pyrimidine synthesis (registered by synthetase) will reflect dysfunction in OPA1 synthetase may due to dysfunction in GTPase synthesis which necessary for OPA1 repairs and reactivities that will be result of synthesis of Androgen instead of Estrogen and accumulation of purines in the form of Glu in neurons and brain tissues which are the sign of immune toxicity and neuronal toxicity.

**GTPase is basic regulator for OPA1 repair and necessary for Rac1 activities for neuron fiber growth**

That inhibition in GTPase will inhibit OPA1 repairs that will be result of synthetase dysfunction and deficiency in pyrimidine synthesis and in amino acids synthesis that will be result of accumulation of purines in the form of Glu amino acids in brain that will be results of liver failure and deficiency in SESN2 synthesis. The S6K-rich Proline necessary for regulating ATPase and GTPase synthesis which in necessary for Gp-GTP-subunits synthesis for activating Gactin, that Rac1 necessary for catalyze lipids for producing long fatty acids chains which produce Gp-GTP-subunits "fatty Acyl-COAs synthesis" (upon OPA1 enzymes functions) dependent on Proline and hydrophobic acids synthesis for activating Rac1 functions and for activating anti-inflammatory growth upon PLCs and IFNs synthesis.

The kynurenine pathway is the primary route for tryptophan (TGG Trp which is essential amino acid used to build protein) catabolism in the liver, but I would like to give notice that pyrimidine in tryptophan is so imp that if missed or inhibited due to dysfunction in pyrimidine synthesis (regulated by OPA1 synthetase) will be result of accumulation of purines and the codons that will be stop codon which consist of only purines eg (GAA and GAG) , that will be result of stopping various cellular activities including regulated translations and inhibition in anti-inflammatory growth, then will be beginning of Cancer mutations that it's growth is not regulated by basic ribosomal ATPase and GTPase. Where, the availability of oxygen active linkages in Rac1 rich Proline has the ability of changing idle +ve linkages in idle molecules to new active - ve linkages by phosphorylation oxidative processes for producing ROS and long fatty chains. Dis-regulation and or over-activation of kynurenine pathway can lead to immune activation or accumulation of potentially neurotoxic compounds depending on availability of necessary Hydrophobic amino acids factors that are necessary dependents (including availability of Leu, Tyr, Ser) for running kynurenine pathway and for promoting condensation of fatty Acyl-COA which are necessary for SESNs biosynthesis.

So therapeutic development to treat inflammation done by strengthen immune effectiveness (throughout Tyr, Leu, and

necessary Hydrophobic acids synthesis) that are having a fundamental ground of understanding the basis of each biological process started by S6K to PLCs and to IFNs improvement synthesis in each tissue and how proper anti-inflammatory growth can basically start and fully done in proper active pathways.

Proper active Rac1 has so necessary roles in the motor neurons empowerment through Gp-GTP-subunits productions for PLCs and IFNs synthesis Rac1 has the role of controlling motor neurons where, Conditional RAC1 knockout in motor neurons restores H-reflex rate-dependent depression after spinal cord injury [30]. Also, the proper active Rac1 has so necessary roles in the motor neurons empowerment that Dysregulation of Rac or Rho elicits death of motor neurons and activation of these GTPases is altered in the G93A mutant hSOD1 mouse model of amyotrophic [31]. And, Rac acts downstream of integrins and growth factors to promote neuronal survival by repressing c-Jun/Bim-mediated mitochondrial apoptosis [32].

That repressing c-Jun Bim-mediated mitochondrial apoptosis need protected ribosomal codes to be produced for recognizing ub-normal codon protein (where ubnormal codons created by formation of stop codon in uncomplicated genes and subunits that those stop codons can be broken by Rac1 oxidative process for producing ROS and long fatty chains which will be follow the effect of OPA1 enzymes which activated by GTPase for creating the three active G-prorein subunits which are gamma, beta and alpha for running the PLCs and IFNs anti-inflammatory growth and processes) for reactivating proper pathways for re-surviving immune and neuronal activities in proper pathways according to roles ribosomal orders, and protecting tissues from the death of neurons.

Also, due to inhibition in Proline and in hydrophobic acids synthesis will be result of dysfunction in Rac1 Biosynthesis, that will be result of purines accumulation (glutamate accumulation) and begining of the formations of the stop codons in uncompleted genes and in uncompleted subunits lead to mutated genes with stop cordons in cancer tissues then will be followed by the improvement of the hyperammonemia (due to inhibition in aminotransferase) and hepatic failure with dysfunction in aminotransferase Biosynthesis. That Immune-Driven Pathogenesis of Neurotoxicity after Exposure of Cancer [33].

Where, toxicity start by stopping in immune development by stopping their Gp-GTP-subunits subunits development by the formation of the stops codons in their uncompleted chains then will turned tue neuronal activities to down streams till reverse catabolic pathways will begin for degradation. That proper active Rac1 molecules are the main for preventing reverse catabolic pathways and regulate the running of proper anti-inflammatory growth in neuron and immune tissues, and in axon anti-inflammatory developments. That it has been reported that Rac1 has been implicated in the control of cell proliferation, neuronal migration, and axon development [34].

Rac1 has imp roles in neuronal migration through ROS and fatty chains production upon Rac1 effect on inflammatory source , and also Rac1 has the role of axon development through G-prorein-GTP subunits productions (upon activating OPA1 by GTPase production firstly by Rac1 for acting on long fatty chains). Also, implicated in the control of cell proliferation throughout adopting G-prorein-GTP subunits productions for PLCs and IFNs synthesis for anti-inflammatory processes and for anti-inflammatory growth.

That the Rac1 activities are linked by activating ATPase and GTPase productions where ATPase imp for running oxidative processes on inflammatory sources for producing long fatty chains and ROS molecules, while GTPase necessary for activating OPA1 enzymes for acting on long fatty chains for producing Gp-Gamma, then for Gp-GTP-beta, then for GTP-GTP-alpha isoforms subunits synthesis for PLCs and IFNs roductions for running necessary anti-inflammatory processes, where Gp-GTP-alpha productions for running anti-inflammatory Growth and cells proliferation. That it has been reported that, both Rac1 and Rac3 GTPase are important for the development of the nervous system [35].

And, Rac1 regulates self-renewal, survival, and differentiation of telencephalic neural progenitors, and that dysfunctions of Rac1 may lead to primary microcephaly [36]. And, Cdc42Hs and Rac1 GTPases, two Rho family members, leads to the reorganization of the vimentin intermediate filament (IF) network, showing a perinuclear collapse [37]. So, Rac1-(rich Proline)-GTPase has the roles of repairing and activating ribosomes, mitochondrial OPA1 repairs (through GTPase production), and regulate Gactin filaments growth and activities which has own functions of providing an opportune platform for cells with mechanical forces and modulate signal transduction through ATPase secretion for running Gactin functions and signal transduction.

That, Rac1 also controls the filopodia dynamics necessary to explore the environment [38]. That any received signals from surrounding environment will be recognized by proper Rac1 which can create the responds by ROS and fatty chains synthesis +active signals that will produce G-prorein-GTP subunits necessary for creating active responds subunits as PLCs synthesis and IFNs productions (upon OPA1 enzymes effects on fatty chains)for adopting neuronal activities and immune responds toward surroundings environment.

That, as in sensory dendritic protrusions, the actin bundle serves as a flexion detector [39]. That, G actin which basically activated by Rac1 detect flexion that improve by producing ATPase and GTPase that will reactivate Rac1-GTPs subunits productions (fatty Acyl-COA beta and alpha) which are necessary for the renewal of neuronal growth filaments and anti-inflammatory processes and growth. Rac1 rich Proline which promote Rac1-GTPs complexed molecules (upon GTPase production to activate OPA1 effects on long fatty chains) controls various of cell signaling pathways, such as the organization of cytoskeleton, cell proliferations , and promoting anti-inflammatory cycles and growth.

The pro-neuroinflammatory reaction played in particularly by microglia (mediated by Rac1 function) exerts a protective function at early stages of the pathology that can considered as the primary ringing of inflammations due to first steps of disease in vivo. Where, Rac1-GTPase plays a key regulatory function of both actin and microtubule cytoskeletal dynamics. Rac1 is also a crucial regulator of NADPH-dependent membrane oxidase (NOX), a prominent source of reactive oxygen species (ROS), thus having a central role in the inflammatory response and neurotoxicity mediated by microglia [40].

The primary functions of Rac1-rich Proline is to act on inflammatory sources to generate firstly the ROS and pro-inflammatory long fatty chains which can be considered as phorbol esters and long fatty acids chains that will be the substrate for OPA1 enzymes for producing Acyl-COA gamma upon synthetase effects, followed by fatty Acyl-COA beta upon synthase effect, then followed by fatty Acyl-COA alpha production (Gp-GTP-subunits synthesis) for cells and tissue anti-inflammatory growth. Where, The ROS generated by the Rac1-NOX2 axis are then responsible for

TNFα secretion, autocrine and paracrine induction of the pro-inflammatory transcription factor NFκB in co-cultured neurons and neurotoxicity [41]. It has been reported that Active, GTP-bound Rac1 acts both as an adaptor, to ensure correct positioning of p67Phox toward cytb558, and as a player in the electron-transfer reaction [42].

Notice that GTPase cannot play as adaptor but play as a necessary tools for OPA1 repairs for activating thé OPA1 enzymes which promote fatty Acyl-COAs isoforms (G-proreins-GTP subunits) synthesis for improving anti-inflammatory protection and anti-inflammatory growth through PLCs and IFNs production, but that electrons transfer are upon the active Rac1-rich Proline effect on inflammatory sources for producing ROS and long fatty chains which will be the substrate for OPA1 enzymes for producing faty Acyl-COAs isoforms where each isoform will promote its own PLC subunits and its own active IFN subunits too as PLCγ1, PLCγ2, then PLC-alpha for cells and tissue growth for strengthen anti-inflammatory cycles and growth, eg Acyl-COA gamma will produce IFN-Gamma, but Acyl-COA beta will promote IFN-beta synthesis, then Acyl-COA alpha will promote IFN-alpha for anti-inflammatory cells growth.

SESNS synthesis are basically connected to Rac1 functions and both connected to diseases such as diabetes, obesity, neuropathic pain. The Activating transcription factor 6 (ATF6) bound to unfolded protein response elements of SESN2 promoter, transactivated SESN2, and increased SESN2 protein expression [43]. And, the PLCγ2 activates transcriptions factor CREB-dependent transcription in PC12 cells through phosphorylation on Ser a.a [44].

So, Rac1 which has necessary roles in regulating and control transcriptions factors through regulating PLCγ2 and IFN-beta for regulating sestrin synthesis in liver. Rac1 regulates and control the condensation of Acyl-COA beta for G-prorein alpha synthesis necessary for sestrin synthesis. SESN2, is upregulated in cells under hypoxic conditions as well as oxidative stress, DNA damage, endoplasmic reticulum stressor function that basically SESN2 Biosynthesis regulated by Rac1 rich-Proline and availability of aminotransferase for amino acids synthesis that promote Rac1 binding to proteins phosphorylation for growth. Where due to pathogenic signals will activate Rac1 for acting on inflammatory sources for producing long fatty chains and at the same time will activate OPA1 mitochondrial membrane for acting on long fatty chains (by oxidative phosphorylation) for producing Gp-gamma, Gp-beta and Gp-alpha for creating anti-inflammatory responds molecules mediated by activating aminotransferase (regulated by Rac1) for binding with aspartate for Leu synthesis which is necessary for SESN2 activities to be migrated to brain for activating Enkephalin tissue through Leu-pentapeptides and Met pentapeptides synthesis which are necessary for continuing Gp beta activities for anti-inflammatory processes and then for Gp-alpha synthesis which imp for anti-inflammatory growth.

That Rac1 rich Proline regulate of protein phosphorylation due to containment of S6K in Rac1 molecules so Rac1 has the roles of regulating the phosphorylations oxidative process on inflammation molecules for producing phosphorylated long fatty chains and at the same time will activate mitochondrial OPA1 membrane by GTPase synthesis for acting on the phosphorylated fatty chains for producing G-prorein gamma, Gp-beta and Gp-alpha responsible for positive regulation of actin filament polymerization, and neuron maturation for anti-inflammatory growth.

That in other pathway, the Rac1 receives the signals coming from the tissues due to the occurrence of a specific disease problem, that will translates those signals into acting on inflammations by Rac1 for producing long fatty molecules and will migrate to liver for activate aminotransferase to combine with aspartate for leucine synthesis which will activate SESN2 synthesis with Leu for migrating to brain for activating Enkephalin Leu-pentapeptides which is important for brain activity for completing anti-inflammatory processes for activating anti-inflammatory growth. That, it has been reported that SESN2 known as hypoxia-inducible gene 95, is upregulated in cells under hypoxic conditions as well as oxidative stress, DNA damage, endoplasmic reticulum stressor.

SESNS are connected with diseases such as diabetes, obesity, neuropathic pain, epilepsy, and Osteoarthritis [45]. That, means SESN2 synthesis dependent on Rac1 Biosynthesis and functions, that in case of deficiency in pyrimidine kinases production (from mTOR phosphorylation signaling pathways) will be result of Deficiency in Rac1 proper structure and activities (that will have deficiency in Proline and hydrophobic acids) that will reflect decreasing in OPA1 repair and activity that will be result of decreasing in G-proreins subunits productions (fatty Acyl-COAs isoforms) that will affect on liver throughout reductions in SESN2 synthesis lead to reduction in brain activities due to reducing in Leu-pentapeptides and Met-pentapeptides synthesis in the enkephalin tissue that will be result in reduction in the restored memories and reductions in fatty acids chains metabolic pathways that will reflects reduction in hormones synthesis due to reduction in pyrimidine synthesis (which has the sign of Androgen synthesis instead of Estrogen) that will lead to decreasing in the activities of thyroid synthesis (which regulated and activated by estrogen production).

Hydrophobic Amino acids synthesis and Availability in genes and in active subunits are playing important roles in the targeting specific cells tissue that each Rac1 with specific Molecular structure with specific percentage of specific amino acids are having specific functions for promoting their own tissue functions and activities.

**Why dysfunction in thyroid are connected to dysfunction in Rac1 and to dysfunction in proline and in hydrophobic acids synthesis?**

Rac1 and p38 mitogen basically regulate thyroid synthesis, while Thyroid-stimulating hormone and cyclic AMP activate p38 mitogen-activated protein kinase cascade :

Rac1 has the functions of repairing ribosomes and mitochondrial OPA1 repair, and has the function of phosphorylation through binding to protein through running anti-inflammatory growth, that Rac1 has the roles of these producing ATPase for acting on inflammatory source for producing ROS and long fatty chains which upon OPA1 enzymes will produce G-prorein gamma, Gp beta and alpha nuclear molecules where Gp gamma and beta will migrate dependent on their composition of amino acids to thyroid glands for thyroid synthesis that it's primary composition depends on Gp gamma and synthetase functions that give the characters to thyroid of Inflammation and oxidative stress (OS) are closely related processes to thyroid activities.

Also, estrogen has the roles of activating thyroid hormones but that function will be decreased in the deficiency of estrogen synthesis due to deficiency in the pyrimidine kinases production upon deficiency in Ser phosphorylation process that will produce androgen instead of estrogen synthesis where, androgyne depends

on purines kinases synthesis from Thr phosphorylation pathway. Deficiency in Ser, will result of decreasing in cholesterol synthesis which is the substrate for the ROR genes Biosynthesis and the G protein gamma subunits synthesis "regulated by Rac1 effect on inflammations and on repairing OPA1 membrane". So deficiency in pyrimidine kinases will reduce proper production of Rac1 and will decrease the production of G-prorein gamma and beta which necessary for activating thyroid hormones. That, due to deficiency in proline will not produce Rac1 which will be a regular S6K without proper Proline that will not give help to thyroid to the conversion of thyroxine (T4) to triiodothyronine (T3) due to full deficiency in Proline and in active oxygen linkages which respond to stress and signals received from other tissues, that thyroid function will reflect reduction in thyroid function and activities and will not has the Inflammation and oxidative stress related functions.

Thyroid-stimulating hormone and cyclic AMP activate p38 mitogen-activated protein kinase cascade. Involvement of protein kinase A, rac1, and reactive oxygen species [46].

P38 mitogen-activated protein kinases (p38-MAPKs) are activated by cytokines, cellular stresses, growth factors, and hormones. We show here that p38-MAPKs are activated upon stimulation by thyroid-stimulating hormone (TSH) or cAMP. TSH caused the phosphorylation of p38-MAPK..

The two thyroid hormones, thyroxine (3,5,3′,5′-tetraiodothyronine) and 3,5,3′-triiodothyronine, are formed by the addition of iodine to an amino acid (tyrosine) component of a glycoprotein which is Gp-beta (not Gp alpha) where binding of iodine with Gp alpha will increase the thyroid growth and size.

Thyroid cancer characterized by decreasing or Deficiency in proline in Rac1 that will activate more Gp alpha with mutated Gp-gamma 1 (which promoted by synthetase) and Gp-beta (which promoted by synthase) that will characterize more growth in gland but with decreasing in anti-inflammatory responds (due to mutated Gp gamma) compared to the normal Gp-alpha which normally promoted by phospholipase from normal G-prorein-gamma which normally produced from normal Rac1 rich Proline.

Thyroid hormones (TH) which is Gp-beta can modulate growth, development and differentiation and metabolic processes through activating their receptors upon OPA1 synthase and phospholipase for modulating other functions as promoting Plcγ2 and IFN beta which promote PLC-alpha for restore calcium during bone growth. Thyroid hormone are Regulated by Rac1 and then by Gp-gamma where increasing in stress will activate the producing of Gp-gamma with more energy that will stimulate the activation of Gp-beta production upon synthase effect then Gp-alpha productions upon phospholipase effects for anti-inflammatory growth.

Decreasing in proline will decrease in stimulating OPA1 activity that will tend the gland to be as other regular tissue increases in size and in alpha genes transcription.

## Conclusion

Rac1 (as considered as S6K rich Proline) are the basis "as mentioned before" necessary for reactivation of ribosomes, and for G-actin reactivation that necessary for neuronal growth. Why Rac1 is considered as S6K molecules it prefère to contains this preferred type of active rich Proline amino acids??

Is it because Proline is able to activate the ROS and ATPase synthesis (that ATPase need to be activated by purines kinases contained in S6K1 molecules) during acting on inflammatory sources for producing pro-inflammatory molecules which considered as long fatty acids chains, then will produce GTPase which will activate OPA1 repairs for activating the fatty Acyl-COAs isoforms (upon the effect of OPA1 enzymes on long fatty acids chains) that will start for regulating the formation of both Plcγ2 and IFNs isoforms that will activate the anti-inflammatory processes (for defeating the microbe producing active subunits and improving anti-inflammatory growth), and activating inflammatory processes for re-growth stationary tissues on the new conditions of anti-inflammatory conditions for resists the source of inflammations which previously damaged tissues, that can be discussed as anti-inflammatory growth for cells protection and resistance which firstly regulated by Rac1 with rich specified active Proline amino acids and with specified necessary hydrophobic amino acids that will have the roles of activating G-actin filaments and ribosomes repair for producing own ATPase and GTPase upon their Activities, where GTPase required for Rac1 activities and for OPA1 repair for running their own proper functions that are necessary for promoting fatty Acyl-COA isoforms synthesis which are responsible for regulating each of PLCs isoforms and IFNs isoforms productions for improving the growth of anti-inflammatory molecules for the growth of new cells and new tissues.

So Rac1 as rich of Proline as are having the most important responsibilities for immune and for neuronal improvement for improving their anti-inflammatory status and growth through promoting both PLCs and IFNs isoforms synthesis for tissues resistance and protection, as inhibition in Rac1 rich Proline proper synthesis will be the main reasons for immune and neuronal toxicity. Also the Rac1 can activate G-actin bundle for acts as a flexor reagent through promoting and activating fatty Acyl-COAs isoforms synthesis for new neuronal flexible growth eg for cartilage synthesis which regulated by Proline availability. We need more Studies that improve the raising of the efficiency of the Rac1 by increasing Proline whether by increasing effective hydrophobic acids including Proline or by availability of vitamin D which increases the efficiency of Rac1 by increasing Proline activities. Increasing Rac1 effectiveness can delete and eliminates neurotoxicity and immune toxicity by increasing effeceincy of Gactin and neuron growth and at the same time helps the increasing of PLCs and TXA2 synthesis.

The lack of proline synthesis leads to a deficiency in the synthesis of important hydrophobic amino acids, which leads to a deficiency in the restoration of both ribosomes and mitochondria and that lead to deficiency in the synthesis of each of ATPase and GTPase that will lead to deficiency in the synthesis of G-prorein-GTP-subunits that will lead to deficiency in both of PLCs and IFNs synthesis , and this leads to osteoporosis, diabetes, blood cancers, and a deficiency in TXA-2 , which leads to the immune toxicity and the toxicity of neuronal tissues that can reflect paralysis in restoring memories from the side of the brain and severe Deficiency In brain activity, where all of those previous Syndrome depends on the percentage of deficiency of each step and the number of cells cycles that depend on it on that part of the deficiencies.

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