Research Article

Sestrin is the Main Active Carrier Tool for Leu Cycles Activities, with AMPK and TOR Proteins Activities. Patients with Diabetes and Atrial Fibrillation are Lacking the Availabilities of Sestrins_Leu Carrier Activities.

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Abstract

Sestrins is the active Leu carrier tool (CLCT) for the activation, regulation, and conservator for meta anabolic energy for doing the stimulated work or exercise for the favor of immune efficiency, that help meta_anabolic processes which is the anabolic processes with generating energy for the favor of doing that exercise or works and in the same time for the favor of anabolic processes for whole neuron and hepatic cells eg during stimulating cells for specific exercise, Leu pentapeptides activities will be stimulated and AMPK with TOR protein synthesis will be activated for sestrinley carrier tools synthesis then will activate PPARs for proliferation for the imp genes, and AMPK with TOR protein for conserving energy and meta anabolic pathways for the favor of neuron cells and hepatic cells efficiency for completing the potential works in a proper active way for mentioning neuron cells effectively.

Introduction

Sestrin structure revealed three functional sites for each of its identified activities: mTOR regulation, ROS suppression and leucine binding.

Sesn3 insulin-sensitizing effect is largely independent of AMPK. Biochemical analysis reveals that Sesn3 interacts with "but not activate" mTORC2 and subsequently stimulates Akt phosphorylation at Ser473. These findings suggest that Sesn3 can activate Akt via binding to mTORC2 "to stop and block its inhibitory activities to ATPase" to re-stimulate phosphorylation again through ATPase loops in G-actin filaments for Leu functions cycles which are mobile controlled and done by sestrin carriers to regulate hepatic insulin sensitivity and glucose metabolism.

Two protein kinases, Target of Rapamycin (TOR) and AMP-activated protein kinase (AMPK), are central regulators of aging that are often found to be malfunctioned in many human diseases and play a role in cancer, diabetes, neuro_degeneration, and other syndromes. Strikingly, AMPK directly activates the mammalian target of rapamycin (mTOR) activity, indicating that these proteins have overlapping binding functions together to facilitate and accelerate sestrin Lue carrier protected structures functions, and both mTOR with AMPK and sestrin with Leu are involved in the same pathways.

The proteins involved in the AMPK has two necessary functions: one is activating overlapping the TOR for acceleration the whole molecules of sestrin_Leu carries.

Conversely, as Sestrin upregulation mimics both molecular and physiological effects of exercise, suggesting that it could be a major effector and energy conservator of exercise meta_anabolism.

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Such eg of the major effector and energy conservators of exercise and anabolic cycles are sestrins which have three functional sites for each of its identified activities: mTOR regulation, AMPK suppression and leucine binding & carrier functions.

Materials

Sestrin, Leu amino acid, AMPK protein, TOR protein, G-actin filaments isoforms, endothelin_1, TNF-α, TGF-β, NFκB, PPARs. Leu_pentapeptide and methionine pentapeptides, G-protein.

Aromatase promotes and ribosomal ATPase regulating the AMPK protein and TOR protein synthesis and regulating the Leu pentapeptides for sestrin synthesis and production.

Deficiency in Leu cycles activities due to a deficiency in sestrin-Leu carrier activities, or due to deficiency in Leu pentapeptides functions from enkephalin in the brain, in cells, and Thrombin, with a regular appearance in TNF-α, TGF-β, will activate the platelet aggregations and activities. Only when TGF-B is lacking Leu functions activities or lacking the sestrin_Leu carriers activities and their active linkages, will stimulate endothelin-1 productions throughout the expression of the NF-κB" from the sick TGF-B.

Specific AMPK protein and Sestrins_Leu carrier have specificity characteristics for only Leu cycles and functions, started to be synthesized from Leu pentapeptides in enkephalin in brain tissue.

Acetylcholine in the brain is main for activating G_protein synthesis and functions for activating sestrin synthesis "and other immune response to cells" for bind to Leu pentapeptides and to be bind with AMPK protein for more specificity to Leu function pathway, then bind during its pathways to mTOR which varies according to availabilities of protein kinase and according to the lue function pathway for the specific potential job which can be for accelerating specific exercise, arteries functions including running blood fluidity in arteries and capillaries, and movements and for lue cycles functions for specific Mata_anabolic processes eg the including of antigen synthesis, alpha subunits activities, aromatase Production and activities, and hormone re_synthesis for completing specific potential or exercise work.

So I can say that sestrin is a specific carrier tool for activating Leu cycle functions as a response to a specific tissue or cells messages to the brain, and at the same time is a protector for Leu amino acids activities in the brain, in neurons and specific tissue cells, but its functions will stop

or reduced if rapamycin or other inhibitors factors will found in more percentages than the ATPase in actin loops or more than ATPase activities in ribosomal structures percentage in vivo.

The AMPK and Sestrin Leu carrier and protector has strong specific composition related to Leu cycles pathways functions, and I will discuss that relation in composition later. Like valine and isoleucine, leucine is branched-chain amino acid. And also is so imp to remember that The primary metabolic end products of some steps of leucine metabolism are acetyl-CoA and acetoacetate which can be reactivated acetylcholine and G-protein again for brain activities; consequently, Leu is one of the two exclusively ketogenic amino acids, with lysine being the other.

Sestrin 1–3, are encoded by three separate chromosomal loci, The abundance of Sestrins is relatively low in resting cells but environmental and metabolic stresses induce their expression by activating several transcription factors, including p53, forkhead box O (FoxO), CCAAT-enhancer-binding protein (c/EBP). Cysteine is found in sestrin isoform2, whereas erythroid nuclear factor is needed for sestrin expression.

Enkephalin has been found, one containing leucine ("leu"), and the other containing methionine ("met"):
_Met-enkephalin is Tyr-Gly-Gly-Phe-Met.

_Leu-enkephalin has: Tyr-Gly-Gly-Phe-Leu

Under stress and disturbance in the regularity of the acetylcholine cycles, it leads to productions of genes & pentapeptides. The formation of these amino acids chain in table 1, in the proper availabilities of GTPase and AMPK protein and activation of cytochrome and ATPase in vivo, can be a good activator for Leu pentapeptides productions and functions, and activator for the Expressions of Sestrins: Tyr, Cys, Val, Gly, Gly, Phe, Leu Ser, Arg, Cys, Gly, Phe, Leu, Ala, Ser, Tyr, Gly, Gly, Phe, Val, Leu Cys, Ser, Val, Arg, Ser, Gly, Gly, Phe, Leu.

Those amino acids chain can have specific promotors that will stimulate aromatase to start acting for reactivate mRNAs& TRNAs productions for sestrin synthesis.

Aromatase, which is the key enzyme for many hormones and genes carriers productions, is comprised of at least ten partially tissue-selective and alternatively used promoters. Those promoters regulated by distinct G_actin & AMPK signaling pathways to stimulate aromatase expression then will be controlled by ATPase & aromatase formation and G-actin peptides

isoforms functions, then stimulations the ET-1 productions will follow the aromatase activities, ATPase activities, and sestrin production, that consequently will reactivate the MAPK pathways & PPARs pathways activities for PPARs genes proliferation functions via recruitment of various transcription processes for sestrin_Leu carriers production.

A shift in aromatase promoter that responsible for the excess of some imp genes production "eg: estrogen" seen in fibroblasts surrounding malignant epithelial cells, indicating the strong relation between roots of hormones & genes synthesis and G_actin with endothelin-1 stimulation functions.

Endothelin-1 is fully controlled by G_actin isoforms stimulated activities and is both considered to be the main composition of the vascular system. That endothelin-1 can be found in arteries and veins, and it's presence functions are to functioning toxic compounds and molecules to be lysis and carried to different cycles and different excreted canals as in kidney or epidermal pores.

Endothelin-1 is found more in Veins to control and protect arteries and aortic functions, through removing most of toxic cpds and molecules, and act on inflammation products which found in the bloodstream in Veins, which can affect on arteries flexibilities functions, and can affect on blood fluidity.

That Endothelins are considered as a strong regulator of vascular tone. Three isoforms of endothelin which are considered as a potent vasoconstrictor. In addition to the effects of ET-1 on vascular smooth muscle cells, the peptide is increasingly recognized as a pro-inflammatory cytokine "because of its functions for lysis & functioning the inflammation content", that is the reason of ET-1 causes platelet aggregation and involved in pro-inflammatory cytokines.

The amino acids composition and their arrangements in endothelin-1 active molecules are playing the main imp roles of endothelin-1 activities, that molecular composition of ET-1 contain 21 amino acids that have in between the same amino acids in Leu pentapeptides, those 21 amino acids in ET-1 are : H-Cys(1)-Ser-Cys(2)-Ser-Ser-Leu-Asp-Met—Lys-Glu-Cys(2)-Val-"Tyr-Phe-Cys(1)-Leu"-Asp-His-Ile-Ile-Trp-OH.

Inflammatory cytokine ET-1 is typically regarded as a smooth muscle spasmogen. Infections are most often associated with the release of pyrogens that include endotoxin and cause the sign of inflammation, shock, and organ failure, and can which disrupt the function of the hypothalamus and enkephalin pentapeptides cycles activities in the brain, that stimulate G_actin isoforms and ET-1 isoforms production activities.

Deficiency or reduction in Leu functions activities with a reduction in ATPase and MAPK pathways can lead to inflammations that can stimulate the increase in ET-1 activities for lysis and functioning inflammations contents.

Patients with diabetes and atrial fibrillation are lacing the Leu cycle activities whether through sestrin_Leu carrier activities or antigen activities or G_actin isoforms functions activities.

Note that: Methionine pentapeptides cycles activities in case of deficiency in Leu pentapeptides activities from enkephalin in the brain can Increase the thrombin formation and activate hepatic stellate cells and promote liver fibrosis, that methionine pentapeptides functions mainly related to and depending on sulfur activities that responsible for tissue synthesis, but primary followed the Leu -pentapeptides activities. Also, the proper activities of brain Leu_pentapeptides can increase thrombin and activate hepatic cells with great careful proliferations control for the favor of all immune, through increasing sestrin-Leu carrier molecules activities with the help of AMPK and active TOR protein in the same active sestrin_Leu carrier tool.

The transcription factor NF-κB is a central mediate inflammation with multiple links to thrombotic processes. That Deficiency in Leu cycles activities due to deficiency in sestrin-Leu carrier activities, or due to deficiency in Leu pentapeptides from enkephalin in the brain in cells and Thrombin, with a regular appearance in TNF-α, TGF-β, will activate the platelets aggregations and activities, "but only when TGF-B is lacking Leu functions activities or lacking the sestrin_Leu carriers activities and their active linkages", thus will stimulate ET-1 productions "by expression of the NF-κB" from the sick TGF-B which lack sestrin Leu active linkages from endothelial cells that with the activated MAPK pathways or active AMPK protein with mTOR active protein will activate PPARs functions for blood cells synthesis, and will activate endothelin-1 for re functioning the inflammation contents for protecting arteries functions neuron and heart from pieces of information toxicities and their results of blockage the capillaries and arteries.

In thrombo-inflammatory processes. Cells that lack the main of Leu cycles activities "whether with Sestrins or without" express NF-κB from TGF-B, that mediates important functions in cellular interactions, cell survival, chemokines. Also, blood platelets, as a nucleated cell, contain NF-κB family members that normally contain Leu in specific active arrangements "for running the Leu cycles activities whether through tRNAs synthesis or mRNA productions" that their corresponding signaling linkages and molecules are involved in platelet activation.

As blood platelets lose that Leu cycles activities or loose sestrin – Leu carrier function activities as NF-κB will be formed from TGF-β which lack Leu amino acid activities, that will stimulate

endothelin-1 activities then will stimulate the MAPK pathways for functioning inflammation products.

Paracrine signaling from endothelial cells will be stimulated and activated by NF-κB production (which exists from cells that lack Leu cycles function activities) in vascular smooth muscle cells and in interstitium that will cause a phenotypic switch to a "synthetic" state to stimulate MAPK activities.

Sepsis is an important example of such deficiency of sestrin-Leu carrier tools and deficiency of Leu functions activities in blood, in hormones, and cells contents leading to severe coagulopathies.NF-κB is critically involved in these pathophysiological processes as it induces both inflammatory and thrombotic responses.

Endothelin-1 mediates it's functions effects through G-protein–coupled receptors "which necessary for lue pentapeptides activities and acetylcholine functions ", and generates ROS which will be used in and by Sestrin-Leu carriers, and also ET-1 through its acting on inflammations can contribute oxidative stress through activation of the MAPK pathway and vascular NADPH oxidase.

Now, my question is:

Why diabetes is characterized by an increase in endosylline 1, with decreasing in PPARs genes proliferations functions?

First, PPARs activities are depending on MAPK pathways which are strongly related to and depending on sestrin – Leu carrier activities (SLCA),

That when SLCA is reduced or inhibited or reduced will lead to a reduction in AMPK protein activities that will lead to reductions in PPARs activities.

Peroxisome proliferator-activated receptors (PPARs) are a key role in glucose and lipid metabolism, and active AMPK protein is so necessary for PPARs activities and functions, that PPARs expressed in many cell types including pancreatic beta cells and immune cells, and is dependent on MAPK functions and sestrin – Leu carrier activities that the reductions in MAPK in or and in SLCA will lead to reductions in PPARs activities and reduction in glucose and lipid oxidations metabolism, and at the same time will tend to increase to endothelin-1 due to the stimulation by NF-κB.

One of the effector inhibitor that can inhibit or reduce sestrin-Leu activator carriers (SLAC) functions are the higher activities of Méthionine-pentapeptides activities pathways which are strongly linked and depending on sulfur element functions, started from enkephalin tissue in the brain.

Hypo or hyper activations of mTORC1 with a deficiency in sestrin_Leu activities functions can disrupt hepatocellular homeostasis and damages, that will lead to platelet aggregations, And can be a result of increasing CO2 toxicity in the interstitium and blood, and can be the result of an accumulation of unpolarized molecules in interstitium fluid and capillaries lead to blood clotting in arteries too, and can lead to isolations of those parts of tissue sick cells, but the binding of TOR protein with AMPK protein to Leu in sestrin biological tool will be a great tool for activating the increasing the blood fluidity. That Leu in specific metabolic cycles will convert to acetyl CoA which is a good activator for acetylcholine in brain activities, and also activator for retinol activities.

Sestrin is produced through ordering messages to Leu pentapeptides activities in the brain upon various action eg: stress, works, studies then will migrate across neuron cells to liver cells where sestrin will be fully synthesized to start its full function.

Sestrin the crystal structure revealed that hSesn2 contains two structurally similar subdomains, Sesn-A and Sesn-C. Both subdomains share significant structural homology with the Ralstonia eutropha protein.

The presence of Leu leucine in sestrin with AMPK is also activated & regulates TOR protein and activates the production of AcCoA. In Brief Leucine metabolite CoA can promote TOR and AMPK protein activities which are the master regulations and activations of cell growth, brain functions and lipid metabolism cycle activities.

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