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Mitochondrial Inner Optic Atrophy 1 (*OPA1*) Gene is Necessary for Regulating and Activating Lysosome, Related Orphan Receptor A (*ROR-α*) genes, and *APOL1* Gene Involved in Autophagy Cells for Anti-inflammation Processes, Where *ROR-α* Genes Stored as Lysosomal Security Granules Within Autophagy Cells.

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Abstract

Tumor Necrosis Factor alpha (*TNF-α*) subunits deficiency or the involvement in will lead to Sickle Cell Disease (SCD) which marked by a phenotypic variability and inflammation plays the major role in SCD pathophysiology, which linked strongly to *ROR-α1* genes expression and functions, and also linked to *TNF-α* subunits expressions and. Activities, where *TNF-α* subunits are so essential for anti-inflammation processes and linked to *ROR-α* genes activities and functions, and necessary for regulation of bone homeostasis in several chronic immune and inflammatory joints and tissues diseases. The inhibition of TNFα due to inhibition or variations in *ROR-α* genes lead d to significant inflammations improvements involved in SCD pathophysiology, and also will lead to increasing in Nuclear factor-κB pathways (NFκB) catabolic pathways and any remaining of *TNF-α* will be involved in the NF-κB signaling pathway due to inhibition in their mitochondrial activities. The inhibition or deficiency in presence of Thymine in the Related Orphan Receptor-A (RORA) genes can reflect deficiency in mitochondrial synthetase enzyme (where mitochondrial *OPA1* gene depending on ribosomal genes activities), that'll lead to down activities in *ROR-α* genes functions, and reductions in *TNF-α*, TXA2, and in VEGF-A subunits. Lysosome and *ROR-α* genes are having so necessary functions of preventing G-protein aggregates associated with neuropathies, and preventing blood platelets aggregations depending on mitochondrial activities through producing its active inflammatory enzymes for acting on any toxic inflammation or on any aggregation for producing the active TXA2 subunits which through feedback will reforme VEGF-A alpha subunits where can be stored in or as lysosomal secretory granules.

ROR-α gene is so necessary for anti inflammations where ROR alpha active gene depending on mitochondrial anti inflammatory enzymes (synthase, phospholipase, Cox2 enzymes) and regulated by mitochondrial inner membrane *OPA1* genes activities which are strongly repaired by acyl-CoA:l-acyl-sn-glycero-3-phosphocholine O-acyltransferase. Where acyl-CoA:l-acyl-sn-glycero-3-phosphocholine O-acyltransferase enzyme is so necessary for re-activating brain acetylcholine and for mitochondrial inner membrane repair and protect liver from fibrosis. Reductions in mitochondrial activities will lead to reductions in *ROR-α* genes activities and consequently will lead to reductions in TNF-alpha and in *CYP7A* genes expression and functions (which are locally produced in brain, and in liver), and will lead to a hepatopathy, encephalopathy, a variants of Syndromic Intellectual Disability. Where, *ROR-α* genes are necessary for *CYP7A* genes productions and activities which are necessary for the Conversions of both cholesterol and 27-hydroxycholesterol into bile acids. *ROR-α* genes considered is imp for regulating anti-inflammations procedures and necessary for controlling the conversion of cholesterol and 27-hydroxycholesterol into bile acids and are so essential for liver protections and are so necessary for protection from sickle cells diseases. Where during autophagy activities which contain *APOL1* protein (lipoproteins) will need phospholipase enzyme for activating *APOL1* gene involved in autophagy cells which expressed from mitochondrial membrane for activating the autophagic *APOL1* gene for expressing *ROR-α* genes from the autophagy cells for fast acting on inflammations, where that previous fact reveal "and I consider it as" that *ROR-α* genes are stored within autophagy cells as active lysosomal security granules for fast acting on tumors and on inflammations molecules which are involved with the pathogenesis of various disorders, including cancer, neurodegeneration, and inflammatory diseases. But in the case of deficiency of mitochondrial activities or in case of inhibitions of phospholipase enzyme expressed from mitochondrial membrane will lead to un activating *APOL1* genes lead to inhibition in releasing *ROR-α* gene from autophagy cells and then involved in tumor contents and in interstitium fluid as inactive molecules.

Keywords: Endosomes tissue cells; Lysosome; Tetraspanins; (TXA2) Thromboxane-A2; Vascular Endothelial Growth Factor VEGF-A; Tumor necrosis; Factor – alpha *TNF-α* subunits; Mitochondrial enzymes; Th17 cells; NR1D1; *CYP7A* genes; Related Orphan Receptor-A (*ROR-α*) genes; Nuclear factor (NF-κB); acyl-CoA:l-acyl-sn-glycero-3-phosphocholine O-acyl transferase (mitochondrial inner membrane repair enzyme "MIMRE"); Apolipoprotein L1_*APOL1* gene; Optic Atrophy 1 (*OPA1*) gene

Introduction

Endosome and lysosome compartments are characterized by their morphological and functional properties, that their healthy composi-

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tions and nutritious can be healthy for inner cells components, or can be un-useful or toxic to living cells depend on its molecular compositions and their main feedback origin. Endosomes are typically involved with the filtering and delivering of lipid vesicles including sorted digested amino acids to and from the plasma membrane then to inner cells components. 'Early' endosomes in young ages are close to sites of active endocytosis, where they can act as a recycling or re-functioning and transport signals genes and vesicles budding compartments molecules to and from plasma membrane (which are formed from inner cells) to other specific specialized tissue cells. Thus, endosomes provided with a sorted lipid, protein, and extracellular molecules to be filtered and transmitted for cells metabolism.

Endosomes, have the transport growth factors and signals transmission functions along the axon, provide a rapid genes signals propagations and regulations of signaling cues. Gene that originally in young ages are a active micro alpha subunits where can stimulate PPARs genes from plasma for antigen synthesis and for inner cells nourishing, and are responsible for inner cell nutritious and protections including anti-inflammatory effects and more as receiving molecules to be filtered for inner cells metabolism and then transmitted as active signals transmission, but as age increased as the composition of endosomes from fatty acids and amino acids will increased and contaminated that will include necessary and unnecessary fatty and amino acids and may include +ve cationic molecules that will delay many of endosomes functions and activities Intercellular connections through endosomes and lysosome are through producing exosomes for running specific metabolic processes, and exosome can be considered as signals genes where can be transmitted by endosomes, and are controlled by ROR-α genes functions and by the lysosomal secretory granules activities, which are involved with the pathogenesis of various disorders, including cancer, neuro degeneration, and inflammatory diseases [1]. The overexpression of Orphan nuclear receptor (TR3) in human umbilical vein endothelial cells (HUVECs) resulted in VEGF-A-independent synthesis, survival, and induction of several cell cycle genes activities [2]. Normal endosomes must contains the main receptors for TXA2 subunits, VEGF-A, and TNFα expressions and activations directly or indirectly, that started by producing mRNA which will follow pathways of productions through translations process with the help of stimulators and activators from other sources and factors as ribosimal ATPase, as mitochondrial membrane functions, and lysosomes.

The delay in genes signals transmissions by endosomes can cause tumour synthesis in specific tissue and can cause capillaries blockage, that can be due to increasing in cationic positive elements and linkages which can cause idle and inactivities to some active sites in gene, that will increase the possibility of neutral inactive linkages, and will be the source of distributing variations and inflammations to all other tissue. As age increased as endosomes and exosomes compositions will contain healthy nutritious components contaminated with Inert idle inactive bonding molecules in a little constituents in their structure, that those idle inactive bonds during heat shock some of those bonds will Brocken then will rapidly formed again in sudden formations fashions that their electrons will be fast rearranged to form new active linkages with new higher active bonding energy value to form an active tetra molecules which is the Tetraspanins.

Moreover, increased in *ROR-α* genes functions will activates AMPK pathways, upregulated antioxidative and will activate anti-inflammatory genes, which ameliorated the symptoms of NASH in the methionine and choline deficient diet mouse model [3,4]. indicating that *ROR-α* gene is so necessary for anti-inflammations where ROR alpha active sites activate and regulate Thromboxane-A2 productions and VEGF-A expressions which depending on mitochondrial anti inflammatory enzymes (synthase, phospholipase, Cox2 enzymes) and regulated by mitochondrial inner membrane *OPA1* genes activities which are strongly repaired by acyl-CoA:l-acyl-sn-glycero-3-phosphocholine O-acyltransferase. Where acyl-CoA:l-acyl-sn-glycero-3-phosphocholine O-acyltransferase enzyme is so necessary for re-activating brain acetylcholine and for mitochondrial inner membrane repair and re-activities, and consequently necessary for *ROR-α* genes re-expressions *OPA1* genes is the main gene in mitochondria, that when stimulated for repair inner and outer mitochondrial membrane will cleavage to produce *L-OPA1* and *s-OPA1* genes, where *s-OPA1* is involved in the outer membrane synthesis upon fusion with *MFN2* gene for activating mitochondria. Where, decreasing in mitochondrial activities will cause

A variants of Syndromic Intellectual Disability with Either Autism or Cerebellar Ataxia [5]. *ROR-α* genes are necessary for *CYP7A* synthesis, which are locally produced in brain and in liver, where necessary in brain to regulate the synthesis of neurosteroids [6]. Where in liver is acting for catalyzing the hydroxyl cholesterol in the regulations of cholesterol synthesis [7]. Where A7 alpha-hydroxylation is necessary for conversion of both cholesterol and 27-hydroxycholesterol into bile acids, and the *ROR-α* genes are necessary for *CYP7-α* genes productions and activities which are necessary for the conversion of both cholesterol and 27-hydroxycholesterol into bile acids. *ROR-α* genes considered is imp for controlling the conversion of cholesterol and 27-hydroxycholesterol into bile acids and are so essential for liver protections and are so necessary for protection from sickle cells diseases. Also, deficiency in *ROR-α* gene activities will reflect decreasing in *f*gene activities, and will lead to decreasing in bile acids and lead to decreasing in liver protections from fibrosis and from inflammation [8]. Also, the high decreasing in *ROR-α* genes in human will lead to dramatic increasing in basal expression of NF-κB regulated genes [9]. Due to the high decreasing in TNFα and in VEGF-A subunits productions002E

Literature Review

Tetraspanins characteristically containing 4, 6 or 8 conserved cysteine residues [10]. Which indicate that the Cys (TGT, TGC) is linked to Thr (ACA, ACG) amino acid and is the main imp amino acid for slowing and control Tetraspanins activities in distinct way where Cys present at the head of the game then Thr at the tail of the gene will bonded together for converting the gene to the circled round inactive or in steady position shape, and that bonds only will be broken by phosphorylation process and by increasing polarities by ATPase for practicing their functions. The Tetraspanins genes activities can be stopped or slow down by constructing that linkages between Cys and Thr amino acids, or and between Pro and Gly, and between Tyr and Leu amino acids respectively, and then will cause Twisting, bending and rotating to the gene to slowdown its activities, but to be activated again those linkages between those amino acids have to be broken down to let and allow the gene to be in active straight linear forms again and that will be done by phosphorylation process whether by ribosomal ATPase or by G_actin ATPase or through MAPK pathways. Those necessary amino acids Thr, Tyr, Gly, Gly, Leu and Cys are depending on their pyrimidine functions where their re-synthesis are depending on and controlled by mitochondrial synthetase enzyme which regulates the conversion purines to pyrimidine.

The presence of active cysteine with Tyr, Gly, Gly Leu and Thr

amino acids in the exosomes and in Tetraspanins are so necessary directly or indirectly for VEGF-A subunits re-synthesis, and for TNFα synthesis , consequently for endothelin-1 synthesis [11]. Where, Cys, Arg, Tyr, Gly, Gly, Phe, Leu, Ser, Thr are necessary for anti-inflammation cycles through the effect of mitochondrial anti-inflammation enzymes (synthase, phospholipase, Cox2) on inflammations molecules to produce TXA2 subunits, which through feedback will re-produce VEGF-A alpha subunits, and then will resynthesis Endothelin-1 during anti-inflammations cycles and processes, then will re-stimulate PPARs genes activities with MAPK pathways for completing the rest of complete cycles. Also we know that Thr with Cys and Ser with Arg amino acids are so necessary for completing phosphorylation processes in several genes during MPAK pathways which controlled and regulated by ribosimal ATPase activities. Indosomes are imp for regulate metabolic cycles through their specific amino acids arrangements to regulate and running anabolic processes and regulate transmitted genes as signals across its polar active receptors in a controlled limited steps depending on ribosomal activities and on surrounding stimulating active sources and factors. As I reported before that the increasing in mitochondrial synthase, phospholipase, and cox2 enzymes will lead to increasing in TXA2 alpha subunits expressions which will lead to increasing in anti-inflammation process then through feedback will lead to increasing for VEGF-A alpha subunits re-synthesis and, then will stimulate PPARs and MPAK pathways activities. As VEGF-A subunits and TNFa synthesised as VEGF-B will start to produced under controlling of their VEGF-alpha subunits which will lead to decreasing in Nuclear factor (NF-κB).catabolic processes, eg in joints, and in muscles. The more of TXA2 and VEGF-A alpha subunits productions, the more possibilities of can be restored in cells as a granules to be ready for safety and security for acting as anti-inflammatory tools on microbe toxic molecules and on inflammations molecules, where can be stored in inner cells as lysosomes secretory granules. T cells and many specific tissue cells are restored their TXA2 and VEGF-A alpha subunits as a lysosomal secretory granules in their inner components. T Cells kill their targets by releasing very potent active cyto-high energy proteins released from their stored granules which characterized as lysosomal secretory organelles. The accurate killing is assured by a vectorial stimulation to secretory lysosomes along microtubules and focused secretion within the immunological synapse [12]. Retinoic acid-related orphan receptor α (RORα) activities has a major roles in various biological metabolic processes including the anti-inflammation processes, and involved in autophagy cells, where, retinoic acid-related orphan receptor α (RORα) controls the inflammatory signaling network [13].

ROR-α genes involved in lipid metabolism where is controlled by mitochondrial phospholipase enzymes (which is necessary for activating *APOL1* gene which involved in autophagy cells synthesis) for producing apolipoproteins, where *ROR-α* genes are produced by autophagy cells for acting on inflammations, and also *ROR-α* genes involved in the regulation of hepatic glucose metabolism, where is necessary for hepatic activities and is necessary for sestrin-Leu carrier synthesis and activities during hepatic metabolic activities, that is necessary for PPARs genes activation. Also *ROR-α* genes activities depending on Thymine nucleotide resynthesis which regulated by and depending on mitochondrial synthetase enzyme which regulate the pyrimidine synthesis in vivo. Where, the most necessary amino acids in *ROR-α* gene are Ser,, Arg, Tyr, Gly, Gly, Phe Leu, and Thr amino acids, that are necessary for TXA2 and then for VEGF-A subunits productions and activities, where any deletion within the *ROR-α* gene leads to an over-expression of inflammatory cytokines [14]. That reveals the roles of *ROR-α* genes activities in regulations the anti-inflammations processes and cycles. Apolipoproteins is a lipoprotein expressed by *APOL-I* gene that form a trypanosome complex which act as anti-inflammatory tool and has hemoglobin-binding Functions That Controlled by presence of phosphodiesterase and mitochondrial phospholipase enzyme functions.

APOL1 are involved in autophagic cell death in case of inhibitions of mitochondrial phospholipase enzymes activities, where reveal that *APOL1* controlled by mitochondrial phospholipase enzymes. Where over abundance of *APOL1* in the avaliablities of mitochondrial phospholipase enzyme within a cell results in autophagy.Where Autophagy is important for the maintenance of cytoplasmic homeostasis. But, orphan nuclear receptor, RORa, was identified as a direct target gene of p53. Upon DNA damage. And, in the same time, RORα controls inflammatory state of human macrophages [15].

So, as *APOL1* protein is a lipoproteins involved in macrophages synthesis and control inflammation processes and involved in cell death in the cause of dysfunction of mitochondria, and as ROR-alpha has anti-inflammatory effects and involved in DNA damage, as there a strong links between *APOL1* protein and *ROR-α* genes during autophagy activities and upon DNA damage and mitochondria dysfunctions. Where during autophagy activities which contain *APOL1* protein (lipoproteins) will need phospholipase enz expressed from mitochondrial membrane for activating the autophagic lipoproteins (*APOL1* protein) then for producing *ROR-α* genes for acting on inflammations molecules, which I consider and reveal that *ROR-α* genes are stored within autophagy cells as lysosomal security granules which are involved with the pathogenesis of various disorders, including cancer, neuro degeneration, and inflammatory diseases in case of deficiency of mitochondrial activities or in case of inhibitions of phospholipase enzymes which expressed from mitochondrial membrane, which needed for activating *APOL1* gene involved in autophagy cells for producing *ROR-α* genes for fast acting on inflammations molecules.

Lysosomes functions are so essential for degrading G-protein aggregates associated with neuropathies such as Huntington's disease (HD) and are important for regulating cholesterol homeostasis [16]. Where *RORA-α* genes are also necessary for regulating cholesterol too through conversions cholesterol to bile acids and protecting liver from fibrosis and from inflammation thus *ROR-α* genes has strong roles in anti-inflammatory cycles, that indicating that links in function between lysosomes and ROR families. RORα up regulated anti-oxidative and anti-inflammatory genes, which ameliorated the symptoms of NASH in the methionine and choline deficinet, indicating that *ROR-α* gene active sites has strong relations with mitochondrial inner membrane *OPA1* genes which are repaired by acyl-CoA:l-acyl-sn-glycero-3-phosphocholine O-acyl transferase, where that enzyme is so necessary for reactivating brain acetylcholine and for mitochondrial membrane repair and re-activities, consequently, that transferase enzyme necessary for reactivate *ROR-α* genes re-expressions for ameliorated the symptoms of NASH in the methionine and choline deficient. Lysosome and *ROR-α* genes are both having the necessary functions of preventing G-protein aggregates associated with neuropathies, and preventing blood platelets aggregations depending on mitochondrial optimal activities through producing its active inflammatory enzymes for acting on any toxic inflammation or aggregated molecules to produce active TXA2 subunits which can be stored in or as lysosomal secretory granules, and then transmitted with mitochondrial synthase enzymes and phospholipase enzymes as active signals genes or subunits throughout plasma membrane and endosomes to interstitium fluid between cells for acting

on aggregated platelets or G-proteins, and acting on inflammations for producing Thromboxane-A2 then throughout feedback will produce VEGF-A subunits for farther the rest of anti-inflammations cycles activities for reactivate endothelin_1 and G_actin filaments, and removing any other toxicity and impurities from blood vessel.

Note, the lysis of any aggregations whether blood platelets or G-proteins aggregation in vivo will need help of the mitochondrial activities to produce its necessary enzymes for acting on the aggregation as synthase, phospholipase, and Cox2 enzymes, where those enzymes are anti-inflammatory enzymes and are so necessary for acting on any inflammations, where their effects on inflammations molecules will produce TXA2 subunits which through feedbacks will produce VEGF-A subunits for increasing the anti-inflammation processes and for reactivate endothelin_1 re-synthesis and G_actin filaments re-activities. So, lysosomes and *ROR-α* genes functions are linked together and depending on those anti-inflammatory enzymes from mitochondria for lysis the aggregated G-protein, so are having almost same active receptors that can be activated by mitochondrial active enzymes, which are stimulated by inflammations molecules or by G-actin isoforms or by the Tetraspanins activities, where Tetraspanins Functions involved in Regulations of Cellular Signaling [17,18]. When, a decrease in NR1D1 will knockdown cells resulted in the reductions of expressions of lysosomal-associated membrane protein 1, LAMP1, commensurate [13]. (that indicating the direct strong links between NR1D1 and lysosomes), and also will be a result of reductions in VEGF-A subunits productions, then reduction in anti-inflammations processes. The overexpression of Orphan nuclear receptor (TR3) in human umbilical vein endothelial cells (HUVECs) resulted in VEGF-A-independent synthesis, survival, and induction of several cell cycle genes activities [2]. The overexpression of Orphan nuclear receptor (TR3) reflect the increasing in mitochondrial activities and increasing in its synthase, phospholipase, and Cox2 enzymes that reflect increasing of the acting of those enzymes on inflammations molecules that will induce increasing in TXA2 alpha subunits productions, and therefore increasing in its feedback to produce VEGF-A subunits productions, and then increasing in anti-inflammations cycles. TxA2 induces platelet degranulation, depending on the mitochondrial activity . The alpha granules or subunits can Lysis platelet or G-protein aggregation, and then will produce TXA2 subunits for re-complete its anti-inflammation pathways activities). *ROR-α* genes involved in regulating Anti-inflammatory state of human macrophages [9]. And protect liver from inflammations and from fibrosis, and has main roles in activating brain functions against inflammation and toxicity through feeding and activating enkephalin leu pentapeptides or Met pentapeptides and activate many of brain processes to be driven to neuron cells. Role of *TNF-α* subunits are so imp in anti-inflammations through the control of the activation and productions and activities of nuclear factor kappa-B (NF-κB) [1]. Where *TNF-α* roles is controlling NK-kB productions and activities without involving in NK-kB pathways .Where *ROR-α* gene overexpression inhibit proliferation and tumor genesis of glioma cells lines and GSCs via inhibiting *TNF-α* to mediate NF-κB signaling pathway [18]. Where reactivations of regular expressions of ROR-alpha (*ROR-α*) genes functions will stimulate mitochondrial functions which will lead to phospholipase productions for activating lipoprotein for generating GTPase and for activating *ROR-α* genes whether in autophagy or in interstitium fluid, result of reactivation MAPK pathways and PPARs functions for continuing anti-inflammations procedures lead to increase *TNF-α* subunits productions, where in that previous steps will produce *TNF-α* subunits with preventing them to don't mediates NF-κB signaling pathway but only will control TGF-β pathways and activities, (the inhibitions of NFκB uncontrol catabolic pathways will be through preventing *TNF-α* to mediate and involving in NFkB pathways, through increasing *TNF-α* subunits productions and functions that will control TGF-β activities), where increasing in *TNF-α* subunits Will inhibit platelet aggregations and will inhibit the irregular pathogenic tumors in the Perfect mitochondrial and ribosomal idealism activities. Reductions in *TNF-α* subunits productions will reflect deficiency in mitochondria or and ribosomal activities, and will lead to Sickle cell disease (SCD) which marked by a phenotypic variability and inflammation plays the major role in SCD pathophysiology, which linked to RORA1 genes functions and *TNF-α* subunits activities, where *TNF-α* subunits are so essential for anti-inflammation processes, and for regulation of bone homeostasis in several chronic immune and inflammatory joints and tissues diseases. The inhibition of TNFα has led to significant inflammations improvements involved in SCD pathophysiology, and at the same time the inhibition or mutations in RORA-alpha (*ROR-α*) genes will lead to inhibitions in TNFα subunits and inhibitions in its controlled anabolic processes, and also will lead to increasing in NFκB catabolic up-normal pathways with involving the remaining *TNF-α* in NF-κB signaling pathway. Also, any variations or mutations or inhibition in *ROR-α* genes can reflect deficiency and inhibition in mitochondrial synthetase enzyme lead to deficiency in Thymine nucleotides synthesis (which are considered as the Basic configurations of Tyrosine, Leu, Cytosine and many other essential amino acids which are so necessary for basic compositions and configurations of active sites in ROR-alpha (*ROR-α*) genes, *TNF-α* subunits, TXA2 subunits, and VEGF-A subunits, and can reflect a severe deficiency in synthetase with phospholipase and synthases enzymes from mitochondrial membrane activities. *ROR-α* genes has the function of activating AMPK, Moreover, RORα upregulated antioxidative and anti-inflammatory genes, which ameliorated the symptoms of NASH in the methionine and choline deficient diet mouse model [3,4].

As I mentioned before that *ROR-α* genes has the function of activating AMPK, and also RORα genes are activated by mitochondrial functions but can re-stimulate to up regulated antioxidative and anti-inflammatory genes activities. The enzyme acyl-CoA:l-acyl-sn-glycero-3-phosphocholine O-acyltransferase is so necessary for mitochondrial inner membrane *OPA1* genes repair and in the main time is necessary for brain acetylcholine reactivities, where indicated to me that acyl-CoA:l-acyl-sn-glycero-3-phosphocholine O-acyltransferase can stimulate and reactivate the *ROR-α* genes, which can reactivate anti-inflammatory and antioxidants processes through activating PPARs genes functions and MAPK pathways. RORγt and RORα related orphan nuclear receptor (ROR) are expressed in Th17 cells, where The loss of Th17 cell populations has been linked to chronic inflammation and microbial translocation, and those regulatory Th17 cells depend on and controlled by mitochondrial synthase, phospholipase enzymes to regulate anti-inflammations synthesis which Promote Th17 Cells functions [19]. And auto immunity where Th17 cells are so necessary for maintenance of mucosal immunity but only are regulated and controlled by mitochondrial membrane functions through producing its anti-inflammatory enzymes (phospholipase, synthase and COX-2 enzymes), which basically regulated by ribosomal genes and ATPase enzymes. Also, *ROR-α* genes is a regulator of Treg genes responsible for suppressing allergic skin inflammation [3]. Through its roles for regulating and participating in anti-inflammation processes. Localization of *TNF-α* genes are on chromosome 6 (6p21.3) [20]. Where is localized just beside lysosomal secretory granules, that Its basic activity depending on the mitochondrial activities, where mitochondrial synthetase enzyme

regulate the expression of Thymine nucleotides from purines through mitochondrial synthetase enzymes in vivo, and is regulating most or all metabolic cycles directly in males, and indirectly in females, where pyrimidine nucleotides are the main for 1st DNA strand in controlling 2nd DNA strand in males, but pyrimidine is main in the 2nd DNA strand for controlling 1st DNA strand in females where the most nucleotides in 1st DNA strand in females are Gly, Glu, Ala,, Arg, Lys,Thr, Gln,Pro, leu (AGC) and a lesser of Ser nucleotides, where if 1st DNA strand in females contaminated with more pyrimidine nucleotides can lead to males characters or layer can lead to variations of normal genes lead to severe health problems including cancer, so when some mutated active sites 2nd DNA strand dominant on 1st DNA strand in males will cause health problems, and also when some variant active sites in 2nd DNA strand in females will dominated on their corresponding 1st DNA strand will cause problems, means mitochondrial synthase enz is controlled and stimulated by their main ribosomal genes which corresponding to the related Gender [21-27].

Results and Discussion

APOL1 protein is a lipoproteins involved in macrophages synthesis and involved in inflammations processes and also involved in cell death in the cause of dysfunction of mitochondria, where ROR-alpha has anti-inflammatory effects and involved in DNA damage. There a strong links between *APOL1* protein and *ROR-α* genes during autophagy activities and upon DNA damage and mitochondria dysfunctions. Where during autophagy activities which contain *APOL1* protein (lipoproteins) will need phospholipase enz expressed from mitochondrial membrane for activating the autophagic lipoproteins (*APOL1* protein) for producing *ROR-α* genes which involved within autophagy cells for acting on inflammations molecules, which reveal and I consider that ROR-alpha genes are stored within autophagy cells as lysosomal security granules which are involved with the pathogenesis of various disorders, including cancer, neuro degeneration, and inflammatory diseases in the case of deficiency of mitochondrial activities or in case of inhibitions of phospholipase enzymes, which expressed from mitochondrial membrane, which needed for activating *APOL1* gene (which involved in autophagy cells) for producing *ROR-α* genes from autophagy cells for fast acting on inflammations molecules. The anti-inflammatory cycles are conserved with high quality accuracy in healthy tissues, and can start as a full cycles or less fast processes for acting on foreign molecules and on inflammations molecules, whether through Th17 Cells or through mitochondrial synthase, COX-2, and phospholipase (which is necessary for activating *APOL1* gene (the lipoproteins) in autophagy cells for producing *ROR-α* genes from autophagy for acting fast on inflammations molecules and on foreign cells). Enzymes for producing Thromboxane-A2 (TXA2) subunits which through feedback will regenerate VEGF-A subunits productions which will control the endothelin-1 resynthesis and consequently, will reactivate G-actin subunits functions. Over increasing in sulfur and in +ve cationic units in genes and in plasma membrane will be the result of increasing the idle inactive subunits in genes or in plasma, which will be the result of formation the hard and rigid membrane structure, that will delays signals genes transmission between cells and tissues, and will delay metabolic processes pathways including anti inflammations processes, that can be the result of blood clots in vessels, specifically blockage in the capillaries that will isolate those cells regions tissue from being connected to other cells tissue then will lead to tumor synthesis. *ROR-α* genes may are containing Tyr, Ser, Arg, Thr, gln, and Leu, where the optimum active sites nucleotides arrangements in RORA straight active genes will be Ser, Tyr, Gly, Gly,Phe, Leu, Arg which are necessary for feeding and re-activating acetylcholine and enkephalin Leu pentapeptides activities in brain,and will be reactivated by the mitochondrial repair enzyme : acyl-CoA:l-acyl-sn-glycero-3-phosphocholine O-acyltransferase which is so necessary for repair and reactivate mitochondrial inner *OPA1* gene which performs most of mitochondrial activities.

Where decreasing in *RORA-α* gene's activities will reflect decreasing in mitochondrial main *OPA1* gene activities, and reflect decreasing in the mitochondrial repair enzymes and consequently will reflect decreasing in *APOL1* gene activities in autophagy cells. The sharp reduction in *ROR-α* Genes functions in some pathogenic cases will reflect decreasing in mitochondrial activities and deficiency in mitochondrial enzymes expression, and will leads to reductions in TNFα subunits productions, and increasing in the catabolic Nuclear factor (NF-κB) pathways, that will lead to osteoarthritis (OA), and lead to decreasing in anti-inflammation processes and decreasing in immune efficiency. *ROR-α* genes is so necessary for proliferation for regulating sestrin synthesis in liver through mitochondrial activities, but the main enzyme needed to be expressed for previous steps from mitochondria is the synthetase enzyme which necessary for regulating pyrimidines synthesis from purines for regulating Leu synthesis and activities. Where The deficiency in synthetase enzyme and dysfunction in mitochondria will lead to dysfunction in *ROR-α* gene and consequently in sestrin-Leu carrier tool, then dysfunction in the conversion of the cholesterol to bile acids through decreasing in *CYP7A* gene synthesis, which are locally produced in brain and in liver, lead to decreasing in catalyzing the hydroxycholesterol in the regulations of cholesterol synthesis, lead to liver fibrosis, and Atherosclerosis, sickle cells disease and more. Also, as *ROR-α* genes functions control VEGF-A productions and functions, as reduction in RORA alpha genes activities will lead to decreasing in endothelin-1 synthesis and functions lead to increasing in vain blockage and increasing in inflammation molecules in arteries and vain with decreasing in lipid digestions and metabolism that will lead also to precipitation of lipids arteries that can lead to Arteriosclerosis, and cardiovascular disease which are linked to sharp reductions in *RORA-α* genes functions and full activities. As the high cholesterol Increase as conversion to bile acids decrease as precipitation in arteries walls will increase, and then atherosclerosis and heat disease will be the result, and the liver fibrosis will be formed, and the failure in anti inflammation processes will be occurred. Patients with diabetes and atrial fibrillation are lacking the *ROR-α* genes activities and decreasing in *CYP7A* genes synthesis and activities.

Conclusion

ROR-α genes regulates pathologic angiogenesis that are necessary for TNFα subunits productions, therefore are necessary for anti-inflammation cycles and processes, *ROR-α* genes necessary for activating enkephalin Leu pentapeptides, where decreasing in *ROR-α* gene's activities will cause. A variants of Syndromic Intellectual Disability. Active *ROR-α* gene in the presence of mitochondrial optimal activities are so imp for protecting liver from inflammations and from fibrosis, and also are so imp for feeding and activating enkephalin pentapeptides in brain for protection from Intellectual Disability. *ROR-α* genes are so necessary for *CYP7A* genes productions and activities for conversion the cholesterol to bile acids through catalyzing 27-hydroxycholesterol molecules to cholesterol then to bile acids.

Lysosomes functions are so essential for degrading G-protein aggregates where depending on mitochondrial synthase and phospholipase enzymes productivity for acting on aggregation which

considered as inflammation (means is responsible for TXA2 subunits productions), and are also important for regulating cholesterol too, therefore lysosomes functions are so connected and linked to ROR-α genes functions. Overstimulation to mitochondria activities through increasing intake alcoholic molecules will cause Overstimulation to mitochondria to produce synthetase, COX-2, synthase, and phospholipase enzymes, lead to over digestion to lipid and some genes chains, lead to high catabolic processes in tissue cells, and highly digestion to amino acids in some genes, lead to mission of the characteristics of those amino acids in their genes where lead to high conversion of purine to pyrimidine, and then purines nucleotides will be lesser or may disappeared, then Gly, Cys, Arg, Thr, Ser Leu will be mutated to be tri-coded pyrimidine and will be variable in their biological structure, lead to hardening in arteries and myocardium, and can lead to tumor and cancer. If *ROR-α* genes due to any known (or unknown) factors will be mutated will lead to down in liver activities and protection from fibrosis, down in VEGF-A expression, and will decrease the enkephalin pentapeptides activities, and decrease the genes signals transmission, and will lead to reductions in Tetraspanins activities. I would like to give imp note that, Any active genes can found in vivo as a straight linear chain (active genetic thread) , but can be circled or rounded (cell round shape) in a steady the Lethargic or in quiet state, where can be circled through covalent linkages between Tyr and Leu, and through linkages between Arg (AGG) at the head of gene and Ser (TCC) at the end part of the gene, where at the time of activating that gene by phosphorylation those bonds between Arg and Ser will be broken through phosphorylation process lead to the return that gene to its active straight form again. Where the active gene forms are found in straight linear chains in vivo and depend on the stimulations by phosphorylation to be active . That activity which responsible for changing Circ-RNAs forms to linear active RNA L-RNAs is controlled by Ser and Arg linkages and Thr (ACC) and Trp (TGG) linkages and Thr (ACA) and Cys (TGT) linkages, where it's necessary to break those linkages through phosphorylation to convert circ-RNAs to to return to its active L-RNAs forms, but in case of deficiency in phosphorylations the circ-RNA will not be able to penetrate living cell for feeding ribosome, and will be present in cytosol as tiny spherical organelles, where that decreasing of previous mechanism can lead to delaying in some metabolic processes and can lead to pathogenic diseases eg un-abilities of Autophages to be converted to its L-acrive forms that will force them to release their active security lysosomal *ROR-α* gene for acting on inflammation and helping for running other metabolic processes.

Conflict of Interest Statement

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

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