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Synergistic anti-oxidant Actions of Mitochondrial Palatin-like PhosphoLipaseA2Domain-Containing Protein-8(PNPLA8/ iPLA2γ) with the Fatty Acids (FA)-Translocating-SLC-25 Gene Family Transporters with their Sequelae-A Review

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Abstract
Palatin –like PhosphoLipaseA2Domain –Containing Protein-8(PNPLA8)alias Ca^{2+} independent phospholipase A2γ(iPLA2γ)is the one that is restricted to the mitochondrial matrix or peroxisomes where it might demonstrate its individual action of cleaving of the phospholipid side chain from sn1 awa sn2 position, leading to liberation of either saturated FAs or poly unsaturated FAs(PUFA)that include oxidized fatty acids. Furthermore iPLA2γ gets directly activated by H2O2 as well as thus get stimulated by redox signaling or oxidative stress. This redox stimulation allows the anti oxidant synergism with the mitochondrial uncoupling protein(UCPs)or other SLC25 mitochondrial family agents acting as carriers by the FA- modulated protonophoretic action also termed mild uncoupling which results in reduction of mitochondrial superoxide generation. This mode permits for the sustenance of the steady state redox status of the cell. Other than its anti oxidant part here the association of iPLA2γ to lipid peroxidation is reviewed here as iPLA2γ gets alternatively stimulated by cardiolipin hydroperoxides in addition to supposedly by structural changes of the lipid bilayer secondary to lipid peroxidation. Rest of iPLA2γ part are mitochondrial (or peroxisomal) membranes besides the production of particular lipid second messengers. Hence like at the time of FAs β oxidationin case of pancreatic β cells, H2O2 stimulated iPLA2γ provides the G- protein coupled receptor (GPR40)metabotropic receptor for multiplication of FA- stimulated insulin liberation. Moreover the cytoshielding part of iPLA2γ in the heart as well as brain,along with role in brown adipose tissue (BAT) metabolism is further detailed. The major work in this field has been by the groups of Jezek P from Chez and Gross RW, Mancuso DJ gourps. Thus this knowledge gives further insight in unraveling the alterations in lipid metabolism in diseases like obesity, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepapititis (NASH), where ectopic fat deposition and accumulation is behind the pathophysiology of these diseases, besides understanding the severity of generation of APS Syndrome resulting in life threatening conditions.

Keywords: antioxidant synergism; iPLA2γ; mitochondrial uncoupling protein; mitochondrial Adeninw nucleotide translocase (ANT); SLC25 mitochondrial family agents; lipid peroxidation

1. Introduction
Having reviewed the roles of mitochondrial uncoupling proteins extensively in case of getting insight into etiopathogenesis of obesity, along with its associated comorbidities, besides impact of aberration of mitochondrial significant proteins implicated in autophagy, role of CLPP, significance of activation factor 6(ATF6),in human reproduction, along with ageing as well as in pancreatic β cells in diabetes mellitus here we decided to get further insight into the role of these processes implicated in lipid metabolism, roles of various phospholipases in detail and further knowledge in terms of anti-phospholipid syndrome (APS)complications [1-8]. Cellular redox(oxidation as well as reduction considered as complementary processes homeostasis, association with redox controlling along with antioxidant modes might be dependent besides single protein reactions, on cycling or synergistic responses in 2 or greater amount of proteins. As in various kinds of eukaryotic cells in addition to /or tissues of mammals, mitochondria are the major place from where reactive oxygen species(ROS) along with tissues use a big amount of volume, nature got generation of modes that avoid escalated ROS generation. Hence a lot of anti-oxidant systems got evaluated in the mitochondria to crosstalk with the ROS generated within them [9-12].
Controlling modes which ameliorate redox signaling, got further generated phylogenetically [11]. Favouring of redox signaling occurs on mild escalated ROS generation in a particular time period.

Principally pathological generation of Oxidative stress (OS) along with, its implications are separated from the physiological controlling modes, besides by the amount of escalated ROS generation but might be different further by the mode of the reaction as well as the pathways implicated. The OS alias alternative generation of a redox signal can be made sure of by greater propagation of time or by escalated/relatively greater ROS generation, respectively, or via reduction of the /detoxification of the particular ROS species, pointing to reduction of anti-oxidant working. These processes might work together as well as /or at same time.

For Oxidative phosphorylation (OXPHOS) machinery is located in the mitochondria, that got generated to possess antioxidant modes by inheritance. The proton pumping across the inner mitochondrial membrane(IMM)to the intracristal space (ICS) generates the proton motive forceΔp(Δp=Δψm+Δ pH),that gets utilized by the ATP-synthase for the rotation of its membrane c-ring for the generation, of ATP. Mild loss of Δp via a moderate simultaneous H^+ backflow into the mitochondrial matrix, terminal mild uncoupling, thus results in ROS generation (that points to an anti-oxidant working) secondary to earlier liberation of an earlier path that had been retarded for electron transport. This decrease usually occurs in normal circumstances, close to the area termed toxic where superoxide generation takes place within the respiratory chain complexes [10]. Nevertheless, this mild uncoupling can't be efficacious in case of mutated mitochondrial mt DNA yield such suppressions or getting initiated through mutant subunits that get coded via the mt DNA.

A little bit of uncoupling might be controlled by the mitochondrial uncoupling protein(UCP).Moreover, for long we understand that some soluble carriers are located in the mitochondrial inner membrane(IMM),besides the UCPs can yield uniport of negatively charged fatty acid anions [13]. Combined with UCPs they are from the gene SLC2 family of mitochondrial carriers. Actually the ADP/ATP carrier(or adeninenucleotide translocase, ANT) represented the 1st carrier in which H^+ transport via the FA cycling mode got anticipated by Skulachev in 1991 [13]. The capacity of FA for stimulation of ATP-based H^+ transport got recently validated via patch clamp estimations [12], akin to that for UCPs. Either in vivo, or in vitro patch clamp studies further corroborated the idea of a developing FA as well as immediate spatio temporal liberation of FAs molecules within the bilayer of IMM following cleavage from phospholipids(PL's),like cardiolipin (or income like being nonbound from protein carriers, enzymes etc) [14].

Further it has been recalled that the IMM lipids or an inner PL's leaflet of the outer mitochondrial membrane (OMM) become targets for PLA2 [16, 17]. Nonisolated mitochondrial isoforms evaluated earlier got ultimately recalled in the form of PLA2 isoformPNPLA8/iPLA2γ along with possibly further PNPLA9/ IPLA2β.However, why should we think of PL in association with antioxidant action? This is in view that any phospholipase, that might be located in the inter membrane either or in the matrix side of the IMM, like iPLA2γ,might effectively break the mitochondrial PL's as well as liberate free fatty acids(FFA). Secondary to this, mitochondrial iPLA2γ is capable of providing budding FAs for UCP s as well as rest of SLC25 mitochondrial carrier family members. Following these symbiotic protein couples might yield mild liberation of Δp, resulting in reduction of mitochondrial superoxide generation in addition to antioxidant activity [18-21].

Here initially molecular mode of antioxidant synergistic mode that implicates iPLA2γ as well as UCPs along with certain selected SLC25 family proteins is discussed. This is followed by the association of iPLA2γ with particular IMM lipid composition, given by exclusive amount of cardiolipin as well as detail parts of iPLA2γ as well as stimulation by lipid peroxidation. Finally –previously recalled cases of participation of iPLA2γ in antioxidant mode as well as /or cytoprotection in vivo of selected tissues as well as organs.

2. PLA2 Group VI, Palatin -like Phospho Lipase A2 Domain-Containing Proteins (PNPLAs)

2.1Classification of PhosphoLipaseA2

In the genome of mammals, greater than thirty separate PLA2 enzymes were isolated as well as sub grouped into various classes. General overview of some particular concentrate on group VI Intra cellular calcium independent PLA2-Group I-III,V,X along with XII get represented through secretory PLA2 (sPLA2),that gets liberated in the extracellular scenario. Subsequently, usually they aid with the extracellular matrix [ECM] remodeling, with there responses resulting in particular lipid modulators as well as take part in lipid metabolism [22]. None of sPLA2 can be considered as a mitochondrial PLA2. Group IV possesses Ca^{2+}-based as well as arachidonyl particular PLA2 that are located in the cytoplasm. Principally, they might influence the outer PL leaflet of OMM (Fig1)[reviewed in [23].

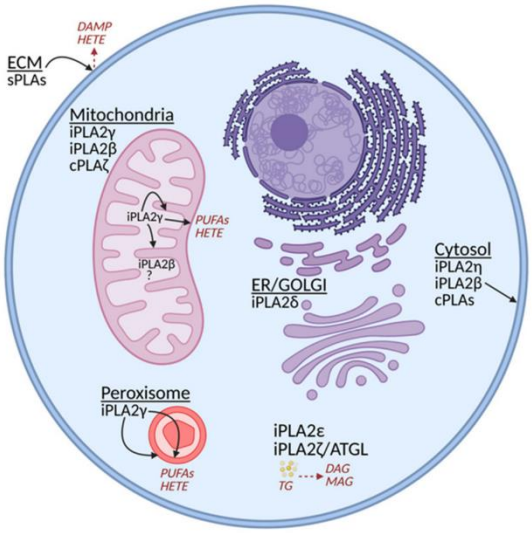

Fig 1: Courtesy ref no-23-Scheme of the distribution of phospholipase A2 family members within the cell. Selected cleavage products are also illustrated. DAG, diacylglycerol; DAMP, Danger-Associated Molecular Pattern; ECM, extracellular matrix; HETE, 12-hydroxyeicosatetraenoic acid; MAG, monoacylglycerol; PUFA, polyunsaturated fatty acid; TG, triglycerides. (The illustration was created with the aid of BioRender.com.)

Group VI has Palatin –like PL Domain –Containing Proteins (PNPLAs) [15], that are Ca^{2+}- independent iPLA possessing lipase (GXGXXG) as well as nucleotide binding (GXGXXG) consensus sequences. Usually PLA2s liberate FAs by liberation of sn2 ester bond of membrane PLs leaving lyso PLs in the membrane. The Group IV phospho lipases A2 further cleave PL acyl chains from both sn1 as well as sn-2 position of PLs. Various isoforms of Group VI iPLA2contain a broad spectrum of action, besides the PLA2s action, that

makes it feasible for certain of these to work as lysophospholipase, transacylase, hydrolase, or thioesterase [15]. They get ubiquitously expressed in all tissues as well as cell kinds while taking part in a lot of events, like PL remodeling, fat catabolism, cell differentiation, Signal transduction along with cell death. The phospholipase in addition to lysophospho lipase PNPLA6/ iPLA2δ is mainly expressed in neurons as well as resides in the endoplasmic reticulum (ER) along with golgi apparatus [24]. The hepatocyte PNPLA3/ iPLA2ε,which is adipose tissue particular PNPLA2/ iPLA2εζ/ATGL, along with ubiquitous PNPLA4/ iPLA2η isoforms further display triglycerides (TG) lipase in addition to acyl glycerol transacylase action [25]. Here we will concentrate on those PLA2s that work basically in mitochondria, Specifically, in parallel with certain other sites. These isoforms further take part in sustaining mitochondrial integrity.

As far as intra cellular residing is concerned, we need to note that most of cytosolic (c PLA2s)enzyme in the Group VI along with Group IV might be efficacious onto the cytosolic surface(outer leaflet)of OMM without having the mitochondria- addressing sequence i.e. without being mitochondrial particular. As compared to that the lone Group VI PLA2s enzyme believed to possess the N-terminal mitochondrial position sequence (other than the peroxisome one) is PNPLA8,alias iPLA2γ [16, 26]. However, a separate broadly evaluated isoform PNPLA9/ iPLA2β had been documented to work in mitochondria [27], in addition to take part in mitochondrial membrane healing subsequent to lipid peroxidation [28]. Currently, the Group IV c PLA2sζ has further been documented to influence mitochondria of the heart [29].

2.2PNPLA9/ iPLA2β phospholipase

The iPLA2β modulates PLA2/ PLA1 as well as lyso phospholipase actions in addition to transacylase action [30]. Besides that thioesterase actions was, illustrated for this enzyme [31]. Furthermore 85kDa of rat iPLA2β protein possesses 751 aminoacids [32]. The GTSGT serine lipase consensus sequence is located following the 8 copies of N-terminal ankyrin repeats. iPLA2β structure was detected [33]. In the documented iPLA2β crystal structure, the open conformation took at the active region, at the place where the dimeric enzyme was not cross talking with the membrane. Open conformation details that both active areas yield adequate space for PL s to reach the active areas. However this does not let interfacial activation, i.e a sharp increase in lipase activity observed when the substrate starts to form an. emulsion, thereby presenting to the enzyme an interfacial area just by membrane contact. The orientation of the ankyrin domains on the outward area of the catalytic region/ membrane interface. The dimer possesses a single calmodulin binding region, whose occupation facilitates hampering by hampering of the catalytic region. In view of the catalytic centers ultimately are placed proximal to the inter face of the 2 monomers. Posit is that the ankyrin repeats cross talks with membrane protein, subject to particular loci. Mimicking the molecular dynamics was done for an anticipated structure of the common PNPLA momoneric enzyme, that illustrated that a stimulating force for the fitting of the enzyme to the membrane is preferred by electrostatic along with nonpolar cross talk [34]. Hence it is inconclusive if iPLA2β gets imported within the mitochondrial matrix [35].

2.3PNPLA8/iPLA2γ phospholipase

Mammalian iPLA2γ mRNA possesses 4 elucidation start areas from where potentially 88, 77-,74-, as well as 63-kda isoforms might be produced. Of these the 63 kDa protein characteristics in the form of peroxisomal was observed [26, 36]. Developing isoforms possessing the N-terminal mitochondrial position sequence get imported within the mitochondrial matrix in which the addressing sequence gets cleaved off. Hence, immediately following import of iPLA2γ might influence the IMM inner leaflet (figure2). What we are not aware is if other kinds of protein import modes let the presence of iPLA2γ in the intracristal space or the outer inter membrane space meaning the layer among OMM as well as inner boundary membrane (IBM; alias the part of IMM composing the cylindrical part which is parallel to the cylindrical OMM of mitochondrial network tubules(fig2).The iPLA2γ mRNA was observed in a lot of human parenchymal tissues, that are skeletal muscle, heart, placenta, brain liver, pancreas [37]. along with in lymphocytes [38].

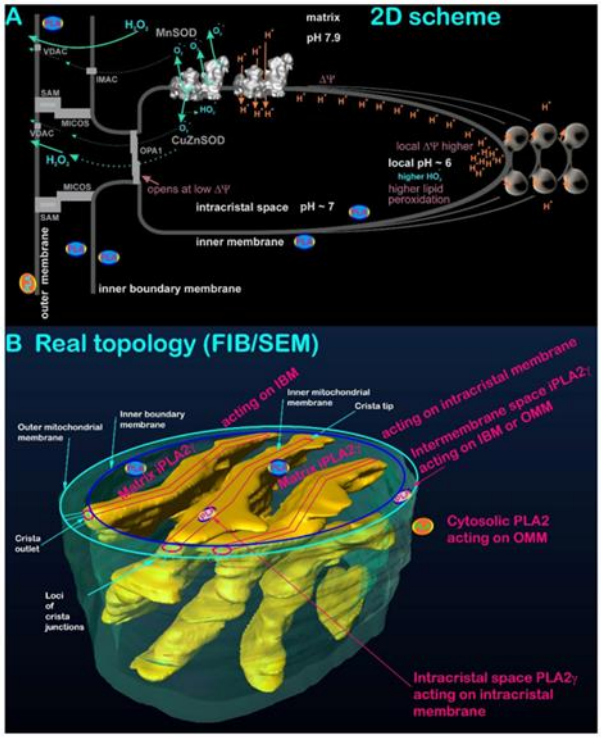

Fig 2: Courtesy ref no-23-(**A**) Traditional 2D scheme of mitochondrial cristae (modified from Reference [41]) and (**B**) actual 3D topology of cristae within a segment of mitochondrial network tubule (OMM, green) with all possible localizations of mitochondrial phospholipase. The FIB/SEM (focused ion beam/scanning electron microscopy) 3D image of the mitochondrial tubule segment of the mitochondrial network in HepG-2 cells was acquired as described in Reference [42]. The 3D image shows cristae, including the intracristal space as rendered by yellow surface lamellae, representing intracristal membranes (an invaginated IMM portion) together with coated proteins of ATP-synthase and respiratory chain supercomplexes. Red lines illustrate the probable location of the membrane (IMM, not in scale), red ellipses depict the crista outlets, in reality, surrounded by MICOS–SAM joined supercomplexes (cf. Panel A), which are indicated only by thin blue lines. Note that intracristal or intermembrane space location for iPLA2γ is hypothetical. The latter location must exist if iPLA2γ participates in remodeling of cardiolipin acyl chains

The iPLA2γ action is unique in sense that it possesses the capacity to cleave PL's acyl chains from both sn1 as well as sn2 position of PL's(but not in dilyso cardiolipin)(figure3).Hence iPLA2γ further cleaves of the saturated side chain [35]. A FA cleavage pattern can point towards a particular PLA2 isoform [20]. Like purified iPLA2γ that gets over expressed was observed to cleave saturated as well as monounsaturated FAs in equal levels from the respective sn1 as well as sn2 position [35]. The sn1 cleavage of PL's having poly unsaturated Fas (PUFA) in the sn2 side chains leaves PUFA sn2 acyl lyso PL's that can get processed through 12-lipoxygenase (12LOX) for generation, of products like 12(s)hydroxyl-eicosatetraenoic (HETE) lysophosphatidyl choline or 12 (s) HETE lysophosphatidyl ethanolamine [39].

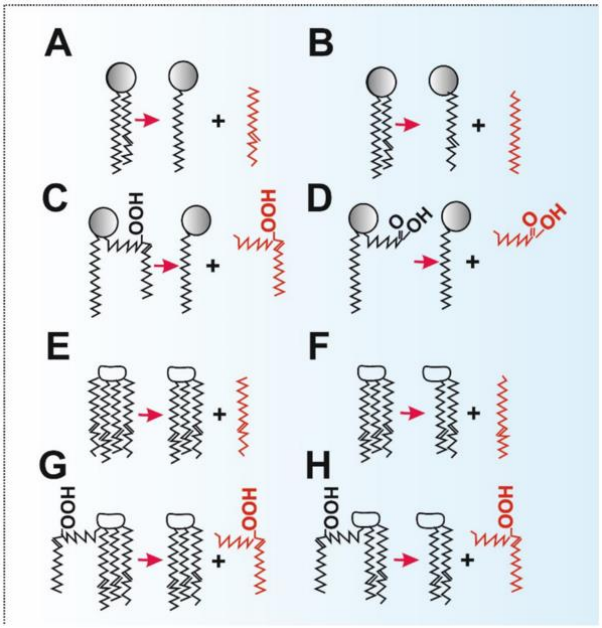

Fig 3: Courtesy ref no-23-(Cleavage modes of iPLA2γ: (**A**) cleavage of unsaturated FA from the sn-2 position (PUFA); (**B**) cleavage of saturated FA from the sn-1 position; (**C**) cleavage of hydroperoxy FA (PUFA after lipid peroxidation) from the sn-2 position; (**D**) cleavage of the shortened alkyl chain (resulting from lipid peroxidation of PUFA and subsequent degradation of the hydroperoxy-alkyl chain); (**E**) cleavage of unsaturated FA (PUFA) from the sn-1 position of cardiolipin; (**F**) cleavage of unsaturated FA (PUFA) from the sn-2 position of monolysocardiolipin; (**G**) cleavage of hydroperoxy FA (PUFA after lipid peroxidation) from the sn-1 position of cardiolipin; (**H**) cleavage of hydroperoxy FA (PUFA after lipid peroxidation) from the sn-2 position of monolysocardiolipin.

These particular lipid species might later work in the form of lipid signaling modulators, significant in immune as well as endothelial cells. Thus we can highlight another part of iPLA2γ that is the generation of lipid signaling molecules. Till we saw the direct activation of iPLA2γ by H2O2 (Fig4) [18-20], the Ca^{2+}- independence of the enzyme action can theoretically be believed that the enzyme is active on encountering particular structural changes in the lipid bilayers. These changes can be secondary to PUFA, cardiolipin, along with hydroxy as well as peroxy groups present in PL FA-side chains along with get mostly reside at the water /lipid interface. During the latter one, lipid hydroperoxides as well as other lipidophilic electrophiles could be posited to crosstalk with the activation area just like as in H2O2 molecules(fig4) [40-42] in fig2.

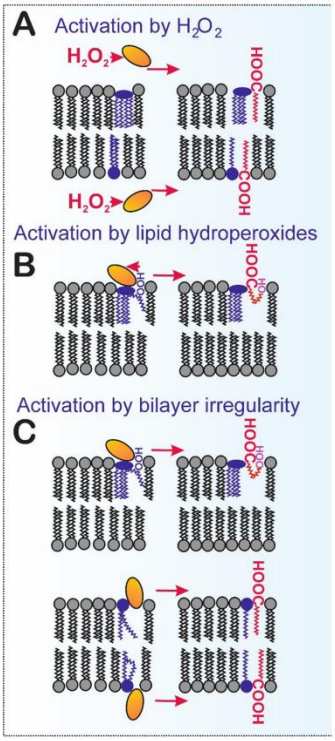

Fig 4: Courtesy ref no-23-(Identified mechanism and hypothetical alternative pathways of iPLA2γ activation. The possible direct redox and indirect redox mechanisms are illustrated. (**A**) Direct activation by H_2O_2 was demonstrated by using recombinant iPLA2γ reconstituted in phospholipid vesicles [19] and isolated rodent mitochondria [17, 18]; (**B**) activation by cardiolipin hydroperoxides. Lipid hydroperoxides and other lipophilic electrophiles could hypothetically interact with the accessible redox-sensitive site similarly to an H_2O_2 molecule, leading to direct oxidation of iPLA2γ thiols [40]. (**C**) Hypothetical activation by structural alteration(s) of the lipid bilayer, caused, for example, by cardiolipin hydroperoxides without direct oxidation of iPLA2γ. These alterations can further be caused by polyunsaturated fatty acids and even hydroxy or peroxy groups existing in phospholipid fatty acyl side-chains and localized at the water/lipid interface.

In contrast to iPLA2β, the structure of iPLA2γ has not been unraveled. The total transcript results in a 88kdaprotein of 782 amino acids in humans. The mutants of iPLA2γSer 483Ala in addition to Asp 627 Ala got documented as non-functional, pointing to Ser- Asp dyads in aiding in the catalytic area [43]. (E)-6 (bromoethylene)-3-(1-naphthalenyl)-2H-tetrahydropyran-2-one also ka R –bromo enol lactate(R-BEL),is A greatly selective inhibitor for iPLA2β [37]. The sustenance of liquid homeostasis of mitochondria along with peroxisomes is agreed upon as a general working of iPLA2γ [17].

iPLA2γ has a necessary part in the hydrolysis of Oxidized cardiolipin, from which particularly 9-hydroxy octadecanoic acid was hydrolyzed [44]. Hence this might yield particular lipid modulators, besides clearing the lipid peroxidation generated products. Despite cleavage of oxidized lipids, a usual function of iPLA2γ might be remodeling of the mitochondrial membranes in addition to the membranes of the peroxisomes. Some studies further verify the part of iPLA2γ in particular generation along with controlling paths of lipid modulators that implicate PUFAs, PUFA-lysoPLs along with monolyso as well as dilyso cardiolipin. Moreover iPLA2γ might work as a key particular controlling nodule in these specific pathways. Like in this way iPLA2γ was pointed

to prostaglandin generation in skeletal muscle [45]. Recently it got illustrated that high fat diet (HFD) stimulates liver iPLA2γ, producing eicosanoids (particularly 12-HETE), resulting in mitochondrial Impairment in addition to muscle, liver cell demise [46].

2.3bRedox stimulation of iPLA2γ

An important crucial parameter needed for the working in addition to antioxidant effect of iPLA2γ is its redox stimulation. The iPLA2γ was documented to get directly stimulated by H202, thus it might get stimulated by redox signaling along with oxidative stress (OS) [18-20]. Following redox stimulation, the antioxidant complementary action of UCP along with iPLA2γ or other family members of SLC25 along with iPLA2γ result in mild loss of $\Delta\psi_m$. Hence mitochondrial superoxide generation decreases in addition to coming back to the cell redox situation to the position before the redox stimulation(figure5).At the time of this event, simultaneously liberated unsaturated FA's or PUFAs, along with saturated FA's cross talk with mitochondrial uncoupling proteins or some SLC25 carrier family members, that lets the shifting of FA anions across the membrane [13, 14, 15]. This results in FA cycling on the return of protonated FA's makes sure of the H^+ shift[14,47-50]back towards the mitochondrial matrix((figure5).This results in a mild uncoupling, as well as simultaneously, towards the amelioration of mitochondrial superoxide generation(rev in ref 5).

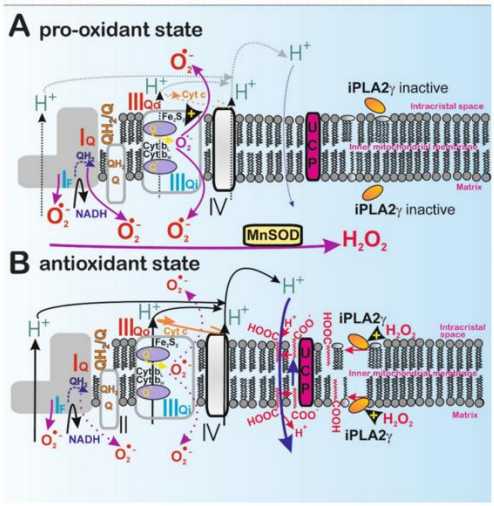

Fig 5: Courtesy ref no-23-(The antioxidant synergy of H_2O_2-activated iPLA2γ and UCP2. (**A**) Pro-oxidant state: low respiration, slow H^+ pumping, and relatively highly coupled state of mitochondria can lead to higher superoxide formation, for example, at sites classified by M. Brand, such as Complex I flavin site I_F, Complex I ubiquinone (Q) site I_Q, and Complex III outer ubiquinone site III_{Qo} [67]. In the absence of a mild uncoupling due to the lack of fatty acids, there is no additional acceleration of H^+ pumping and respiration. (**B**) Antioxidant state: accumulated H_2O_2 (transformed from superoxide by MnSOD) activates the mitochondrial phospholipase iPLA2γ, which subsequently cleaves FAs from phospholipids and cardiolipin of the IMM. The nascent FAs bind to UCP2 and are exported as FA anions from the inner (matrix side) to the outer (crista lumen) intracristal membrane phospholipid leaflet [47, 48, 49]. The subsequent protonation allows FA to cross the lipid bilayer by electroneutral diffusion (flip-flop) back to the matrix, releasing H^+. Note that protons are not conducted by UCP but by protonated FAs. As a result, a moderate H^+ short-circuit of the IMM substantiates mild uncoupling, which immediately accelerates electron transport (respiration), leading to a decrease in superoxide formation [18, 19].

Such mode might further be a part of the repression of the amplitude of continuing redox signaling, like as needed for cytokine generation in the immune cells [10]. Both processes hence comprise the documented antioxidant as well as anti inflammatory synergy of UCP along with iPLA2γ [19, 20].

Tissues possessing lesser excessive expression of different UCP isoforms(UCP1 as well as UCP5)the ANT(ADP/ATP carrier) might play the UCP part [18]. The teamwork of iPLA2γ- ANT needs to be present in all tissues in addition to cells, with utilization of OXPHOS, in view that ANT is omnipotently expressed in addition to the protein expressed in maximum amounts of the IMM[51].as per proof FA's possess an essential part in the H^+ shift that gets modulated by both ANT along with UCP [10, 14, 47-50].

The cyto shielding characteristics of iPLA2γ were pointed for the heart [18], as well as documented earlier in the Kidney podocytes, avoiding glomerular damage [52], along with pancreatic β cells[20],besides human glioblastoma A172cells [53]. Stimulation of iPLA2γ by oxidative stress (OS) was illustrated in myocardial tissue in view of simultaneous hydrolysis of the oxidized cardiolipin [44]. The iPLA2γ was further isolated in the form of membrane potential sensitive PL in liver mitochondria [54]. Having the knowledge of redox –based controlling of iPLA2γ action in addition to the dependency of mitochondrial ROS generation on $\Delta\psi_m$ this event needs more evaluation.

2.3b. Antioxidant Approaches of iPLA2γ as well as mitochondrial uncoupling proteins

1) Elementary fatty acids (FAs)-Spatiotemporal FA Liberation Starts mild uncoupling by UCP's

In the complicated cellular surroundings, fatty acids (FA) might start in addition to get located within the lipid bilayer membranes like IMM as well as OMM, following getting liberated from FA binding proteins or enzymes of FA metabolism, like from the CD36 FA transporter or long chain-acylCo-A Synthetase (ACSL).The other alternate method is FA's get cleaved by mitochondrial PLA2, like iPLA2γ, from PL/that are cardiolipin bilayers of IMM as well as OMM (fig1).

From these findings [14, 20] conclusions were drawn, that mild uncoupling action of UCPs does not get started by the big quantity alias ''bulk'' free fatty acids(FFA) possessed within the IMM, but the budding FA's, meaning FA that get cleaved from PL/that are cardiolipin of IMM. Patch clamp studies of the native IMM of brown adipose tissue (BAT) mitochondria pointed that currents initiated from a high amount of UCP1,based on a calcium independent PLA2 starting [14]. The kind of PLA2 remained nondetermined.

In the studies of Jezek group of insulinoma INS-1E cells with iPLA2γ, they did not find any mild uncoupling secondary to just adding exogenous FA in the cell suspension, that otherwise was present in controls that were transfected with siRNAs [20]. Hence, this latter mode was reasoned with regards to redox stimulation of iPLA2γ,by ROS generated at the time of β oxidation of the exogenous FA added in addition to no capacity of the ''bulk'' FA that were added to the cells for direct induction of UCP2 modulated uncoupling. Further it was validated that the ROS- stimulated mild uncoupling was lacking Subsequent to UCP2 silencing [20].

2) Mode of Uncoupling Protein-modulated Repression of mitochondrial superoxide generation

Mitochondrial uncoupling protein sheds Δp as well as thus

uncouples respiratory chain proton pumping from ATP generation, stimulating the proton backflux into the matrix through the rotating c –ring of the ATP-synthase membrane F_O moiety. This dispersion of Δp can be massive, like in the situation of UCP1 in mitochondria, where UCP1 yields an almost total ‘’thermogenic’’ uncoupling towards less Δp amounts [55]. The words mild uncoupling got introduced in the form of part of membrane-associated systems avoiding superoxide generation on dispersion of Δp only in partial amounts [56]. At the time of this event, the amount of Δp still continues to be sufficiently great to stimulate ATP generation, where the parallel H^+ backflow comprises the uncoupling (H^+ leak).It needs to be highlighted that the degree of H^+ leak across the inner membrane is not-linear, that is subsequent to non-osmic behavior. Since the Δp(mostly estimated as ($\Delta\psi_m$)reduces un-proportionately large alterations in the rate of oxygen getting consumed becomes of obvious to defend the proton motive force (alias energy generated during the transfer of protons/electrons across an energy transducing membrane) [57]. Conversely, at the time of ATP generation when there is high flux of H^+ shift modulated like by uncoupling proteins, might result in only small escalation of respiration, yet the corresponding reduction in $\Delta\psi_m$) would be relatively great [57, 58].

Subsequent to decades of altercation, FA’s are now mutually proved to be totally needed for this mild uncoupling [13, 14, 59]. Thus, independently of the molecular modes implicated, mild uncoupling gets started by FA’s, most probably endogeneously liberated by mitochondrial PLA2.

On local retardation of the electron transport by the respiratory chain, superoxide generation gets escalated [60] (fig5A).This condition takes place under coupled respiration, as the ability of the respiratory chain H^+ pumping is greater in contrast to the H^+ backflow through the c ring of ATP-synthase. In these situations, $\Delta\psi_m$) is great. Thus ROS generation was observed to be significantly potential-based [61].

Reduction in electron transport (respiration) was associated with an event of so called respiratory regulation. In the beginning an escalation of respiration by ADP by definition as the liberation of respiratory regulation. A molecular reasoning for this event was presented by the chemiosmotic posit that pointed that Δp of oxidative phosphorylation is an intermediate that gets utilized by the ATP-synthase for generation of ATP from ADP along with phosphate.

As compared to that, mild uncoupling by FFA’s would further cause reduction of Δp as well as thus ameliorate ROS generation by the respiratory chain (figure5B).On disturbance of the steady state by an extra H^+ backflow (H^+ leak), contributed like by FA –based UCP modulated H^+ shifting, the proton pumping as well as electron transport get lesser hampered by Δp, which exaggerates electron flow at areas, where superoxide generation can occur. Rapid electron transportation hampers the possibility of superoxide generation (figure5B). This continues to be the major philosophy reasoning out why mild uncoupling results in mitigation of mitochondrial superoxide generation. What is Intriguing to notice is that proton conductance by FFA’s in the lack of uncoupling proteins is observed in the planar membranes, that is robustly based on the FA molar fraction in the membrane generating solution [62].

Nevertheless, this mode can’t work when mutations of either complex I or complex III proton pumping machine are present, that automatically hampers proton pumping along electron transport with in an irreversible way respectively. At the time of evolution natures logic worked for crucial ND Subunits of complex I proton pumping in addition to complex III Subunits get encoded by mitochondrial DNA. This is the reason why mild uncoupling cant rescue greater superoxide generation that gets generated secondary to mutations of these mt DNA encoded subunits [63], as well as mild uncoupling cannot rescue greater superoxide generation in the mutator mice (possessing mt DNA polymerase i.e Polγ) [64].

3) Anti-oxidant Symbiotic Association of iPLA2γ as well as Uncoupling Proteins

The separate theories presented above got verified like for the antioxidant Symbiotic association of the mitochondrial Uncoupling Protein UCP2 in addition to mitochondrial phospholipase A2 γ (iPLA2γ [19, 20]. Once the function of these proteins got started, superoxide generation got down regulated. These experiments were depending on the invented ability of iPLA2γ to get redox-activated.

From the experimental proof it is validated the presence of antioxidant synergistic association of iPLA2γ with UCP2 that downregulates oxidative stress in lung and spleen, tissues where UCP2 expression is in high quantities [18]. Hence classically for activation of iPLA2γ,terbutyl hydroperoxide (TBHP) or H2O2 addition is required in identified mitochondria or cultured cells TBHP along with H2O2 stimulate budding FA liberation from mitochondrial membranes, that gets hampered by its stereoisomer S-BEL, pointed that there iPLA2γ takes part. TBHP along with H2O2 result in an enhancement in respiration along with reduction in $\Delta\psi_m$ in mitochondria from control, but not in UCP2 knockout mice. Both alterations are totally hampered by R-BEL, that is a selective inhibitor of Calcium independent phospholipase A2 γ (iPLA2γ) [18, 19]. As an alternative method iPLA2γ activation occurs via palmitoylcarnitine, that can get reasoned out by the H2O2generated in cooperation with the electron transporting flavoprotein: ubiquinone oxido reductase (ETFQAOR) or FA β oxidation.

In case of identified heart mitochondria, the hydroperoxide –started uncoupling gets hampered by carboxytetractyloside along with purine di as well as tri-phosphates, pointing that the mild uncoupling found got initiated from the redox activated iPLA2γ that loans budding FAs for the initiation of FA-based H^+ shifting, that is modulated by ANT1 in addition to UCPs [18]. In akin experiments with utilization of mitochondria identified from tissues that have abundant UCP2 [19], along with insulinoma INS-1E Cells [20], the antioxidant symbiotic association of iPLA2γ as well as UCP2 was illustrated as being based on the isolated redox activation of iPLA2γ.These results validate the mode of H2O2 activated iPLA2γ,resulting in following cleavage of PL’s as well as liberation of free budding FAs which are cycling substrates of UCP2,resulting in mild uncoupling. The subsequent partial dispersion of Δp has been demonstrated to start a direct feedback amelioration of mitochondrial superoxide generation [19-21].

4 Reciprocal impact of mitochondrial as well as cytosolic redox state

In case of tissue where the mitochondrial network makes up a lot of volume of the cell, any transfer in the redox state of the mitochondrial matrix needs to be projected to the cell cytosol or outside of cell as well [9]. Hence, once the reduction

rates of H2O2 in addition to the superoxide generation from the mitochondria to the cytosol get proved, this makes an extra cell antioxidant ability which had been earlier utilized for the detoxification of mitochondrial H2O2 as well as superoxide. This additional detoxification ability can thus work on other cellular events like for slowing of the lipid peroxidation, besides protein along with DNA oxidation. By this method the reduction in mitochondrial ROS source gets spread as antioxidant shielding of the cell in addition to lets for the sustenance of the steady state redox status of the cell.
From the above observations it was posited by Jezek group that a necessary physiological part for the iPLA2γ exists in the total cellular redox homeostasis. The couple iPLA2γ/ UCP lets a feedback down regulation, besides of mitochondrial superoxide generation, as well as of cellular redox status. Hence any prooxidative insult might result in stimulation of iPLA2γ along with initiation of antioxidant effect influencing the full cell. Thus redox controlling starting either from cytosol or mitochondria escalate the amounts of H2O2 or other ROS, that directly cause activation of the mitochondrial iPLA2γ/ UCP. Uncoupling initiates reduction in the generation of mitochondrial superoxide, as well as hence, further the mitochondrial matrix manganese superoxide dismutase generates lesser H2O2. Subsequently the liberation of H2O2 along with superoxide from mitochondrial to cytosol halts, resulting in extra anti oxidant ability that had earlier utilized for the detoxification of mitochondrial part H2O2 as well as superoxide. The extra detoxification abilty thus is reflected in rest of cellular events [19].
In case of earlier published experiments, the problems by blocking iPLA2γ working or abolishing UCP2 (by evaluation of the UCP2 knockout mice),it was observed from these observational studies that both problems escalated acute oxidative stress in the lung and spleen, pointed that the synergistic anti oxidant action of iPLA2γ/ UCP are a part of the significant cytoshielding in addition to anti inflammatory mode of these tissues. Like the mode of iPLA2γ-based UCP2- modulated antioxidant shielding was evaluated with the utilization of lipopolysaccharides (LPS) -stimulated proinflammatory in addition to prooxidative reactions. The subsequent acute implication on the total Oxidative stress got projected by protein carbonylation in the murine lung and spleen mitochondria in addition to tissue homogenates [21]. The hurdles encountered were blockade of iPLA2γ activity by the selective inhibitor R-BEL as well as deletion of UCP2 by genetic method. The documented outcomes agreed with the UCP2 as well as iPLA2γ synergistic anti oxidant mode in these tissues along with corroborate its aid to cytoshielding modes in vivo [21].

5) Mode of Repression of Mitochondrial Superoxide Generation By activity of ANT SLC25 Family proteins

Besides uncoupling proteins, the mitochondrial ANT along with other SLC25 mitochondrial carrier family members alias aspartate/glutamate antiporter as well as the phosphate carrier, are implicated in the uncoupling actions of FAs on mitochondria [13, 50, 65-67]. Particularly, the FAs-initiated respiration, sensitive to carboxyactractyloside, has been found in mitochondria identified from skeletal muscle [65], liver [50, 65, 66], heart [68], Kidney [67], as well as brown adipose tissue (BAT) [69]. Bertholet et al. [13], with the aid of utilization of patch clamp recording of ANT currents directly from the IMM from different mouse tissues. They demonstrated that H^+ transport is an integral function of the mitochondrial ADP/ATP carrier ANT [13]. The ANT modulated H^+ currents need FFA's as well as simulates the H^+ leaks through the UCP1 observed in BAT. The ADP/ATP exchange through ANT negatively controls the H^+ currents, nevertheless, does not totally hamper it. Nevertheless, unlike for UCP1, FAs were pointed to bind within the ANT transportation pathway as cofactors instead of transported species [13]. Nevertheless, more ANT current experimental observations from utilization of recombinant ANT1 that got reconstituted in the planar bilayers documented that ANT1 modulates H^+ transport only in the existence of long chain FAs in addition to that the outcomes validated the FAs cycling mode for H^+ transport [70].
ANT has further been pointed take part in the repression of superoxide generation. It has further been, illustrated that FAs are the natures uncoupling agents that avoid superoxide as well as H2O2 generation by the rat heart mitochondria that have got to be identified as resulting in oxidation of succinate, along with carboxyactractyloside ameliorates the action of Fas [68].

6 Synergistic Anti-oxidant Action of iPLA2γ as well as ANT or iPLA2γ as well as Rest SLC25 Family proteins

Since mitochondria in different tissues contain phospholipase A2action, it has been hypothesized that iPLA2γ cleaved FAs might be the primary physiological source of FAs for ANT based H^+ currents [13]. However, the direct proof validating the part of mitochondrial iPLA2 in ANT modulated uncoupling along with anti-oxidant working is occasional. Their outcomes have demonstrated that iPLA2 based enhancement of respiration as well as reduction in $\Delta\psi_m$ is greatly sensitive carboxyactractyloside in addition to that ANT is majorly implicated for uncoupling that gets started by redox sensitive to mitochondrial iPLA2 in case of separated rat heart mitochondria [18].
The putative part of iPLA2 action along with significant FAs on ROS production have further been evaluated via utilization of rat brain mitochondria [71]. The mild uncoupling action was activated by low micromolar amounts of docosahexaenoic acid (DHA), that is a main iPLA2 product in the brain. It got demonstrated, that ANT patially modulated (DHA-stimulated uncoupling as well as by low micromolar DHA amounts cause reduction in ROS production under a particular situation. Nevertheless, this study further documented that racemic BEL, that is a pharmacological inhibitor of iPLA2s might influence harmful actions on energy –based working of mitochondria [71].
Studies conducted by Jarez et al., that used brain mitochondria that had been separated from wild type (WT) along with iPLA2 KO mice, agree with the anti-oxidant synergistic action of iPLA2 as well as ANT in brain. They observed that low micromolar amounts of THBP –stimulated an escalation of respiration in addition to a simultaneous reduction in mitochondrial superoxide along with H2O2 generation. These actions of THBP got totally avoided by bovine serum albumin in addition to hampered by a selective inhibitor of iPLA2s as well as we're lacking in brain mitochondria separated from iPLA2γ KO mice. Furthermore, the THBP –stimulated actions were totally sensitive to carboxyactractyloside, which pointed that there is a primary part played by ANT [72].
Since the PLA2iPLA2γ is a main modulator liberating oxidized aliphatic chains(i.e. hydroperoxy FAs) from

cardiolipin [44], in addition to part played by ANT is in oleate hydroperoxide –stimulated uncoupling [67], Juzarek et al. [23], posited that redox- sensitive iPLA2sin combination with ANT might further possess anti-oxidant working that gets stimulated by mitochondrial lipids peroxidation(fig3 as well as 4).

3. Redox stimulation of iPLA2γ

3.1Direct stimulation of iPLA2γ by oxidants

Regarding the molecular mode of by which H2O2 results in activation of iPLA2γ, both the direct redox in addition to indirect redox modes are probable. Experiments implicating utilization of recombinant iPLA2γ that got reconstituted in phospholipid vesicles demonstrated that hydroperoxides (both H2O2 as well as THBP) have the capacity of activation of iPLA2γ directly, with a half maximum activation constant AC_{50}that is equivalent to 1.5nmol H2O2/nmol of the enzyme [20]. For cultured cells Jezek *et al*. [20], further validated the direct activation of iPLA2γ working by H2O2 [20].

Protein thiols are few classes of biological molecules which H2O2 directly reacts with [73], mitochondria possessing abundant Protein intrathiols, that exceeds the amounts of small molecules thiol pools like glutathione by various times [74]. Redox controlling by thiols shifting has been a long known mode for verification of rapid acclitimization of mitochondrial protein working at post-translational state [88]. Hence thiols that can be accessed (de protonated to originate reactive thiolate anion) aid in reversible oxidation by H2O2 to sulfenic acids. Reactive sulfenic acids can get glutathionylated, generate inter or Intramolecular disulfide bonds, or can get more oxidized to sulfinic acid or further sulfonic acids. Various extra thiol- redox modifications like S-nitrolysation are probable [75]. The direct redox activation might further get progressed by proteins possessing the capacity of SH-relay, like peroxidiredoxins, directly impacting cysteine residues of the enzyme [11, 12, 76].

Furthermore lipid peroxidation along with following decomposition of lipo peroxidation products usually produce reactive electrophiles, that are α,β unsaturated aldehydes, malondialdehyde (MDA), hydroxyl alkenols, oxo alkenols, epoxy alkenols, as well as ketoaldehydes. The nucleophilic amino acid, cysteine, histidine as well as lysine are the commonest modulated lipid obtained electrophiles [77].

As per the computational anticipation, human iPLA2γ possesses Cys 558 as well as Cys714, that have the potentiality to get oxidative modifications. Furthermore mouse iPLA2γ is also counted in the oximouse database that was generated by Chouchani *et al*. [78]. That defines as well as confirms the cysteine redox networks within every tissue(http:// oximouse.hms.harvard.edu/accessed on 19feb 21) Cys 553 as well as or Cys708 of iPLA2γ were revealed to be Oxidized in various tissues of young as well as old mice,that included BAT, lung,spleen, brain that validates the redox modifications of iPLA2γ.

The alternate modulated redox activation might be enforced by the proteins having the capacity of SH-relay, like peroxidiredoxins, so that peroxidiredoxins3 (PRDX3) located in mitochondrial matrix get oxidized initially, shifting this redox signal for oxidation of thiols of iPLA2γ. Additionally, other oxidant species might be posited to crosstalk with the iPLA2γ thiols as well as stimulate the enzyme. Lastly redox activation of the protein kinase modulated signaling pathway, that stimulates iPLA2γ might be feasible. The enzyme activation gets modulated by protein phosphorylation. Such mode was pointed by the stimulation of iPLA2γ in experimental membranous Nephropathy where complement C5b-9 induced glomerular epithelial cells damage [96]. Hence complement- modulated iPLA2γ stimulation gets modulated through extracellular signal – regulated kinase (ERK1/2) as well as p38 phosphorylation or Ser 511 as well as /or Ser 515 possesses a crucial part in the catalytic action along with signaling of iPLA2γ [79].

3.2iPLA2γ vis a vis Lipid hydroperoxides as well as other products of Lipid peroxidation

Lipid peroxidation results in structural changes which interfere with the membrane intactness [80]. The proper hydroperoxides group of lipid hydroperoxides shifts to the lipid water partition as shown by molecular dynamic mimicking [81]. Initial research on the mode of PLA2 catalytic action evaluated lipid peroxidation as well as PLA2 action in liposomes comprising of unsaturated PL's, as well as direct association was observed among the degree of lipid peroxidation in addition to the degree of PL hydrolysis [82]. Sevanian *et al*. [82], concluded that lipid peroxidation generates a smooth enhancement of membrane viscosity, that is correlated with the vesicle being unstable along with escalated PLA2 attack [82]. This can now be thought of as an indirect mode of PLA2 activation, sincelipid peroxidation or alternately, by the local structural changes in the form of a lipid bilayer. Nevertheless, other studies divulged an enhancement of the PLA2 action is mostly secondary to a peroxidized PL molecules in the form of substrates, besides the peroxidation of host lipids does not significantly enhance the rate of hydrolysis of nonoxidized lipids [83]. As shown in fig 4 Hydroperoxide crosstalk with the thiols of iPLA2γ does not essentially require to get modulated only by ''free H2O2''.It can further get modulated by the hydroperoxide groups of FAs esterified in membrane phospholipids. The initial data by Jaburek *et al* [40], demonstrated that lipid hydroperoxides can crosstalk with iPLA2γ, causing akin activation.

Furthermore activation of iPLA2γ by the local Structural changes of lipid bilayer might be present supposedly. This is possible once lipid hydroperoxides had not been reduced on crosstalk with iPLA2γ.Despite the structure of iPLA2γ has not been unraveled, a speculation can be made with regards to its mode of action is akin to that of iPLA2β.In the iPLA2β dimer, both active locations yield an open space for phospholipids that readily reach the active centres. Further posit is that this might get promoted at the loci of lipid bilayers disturbances secondary to hydroperoxy FA as well as hydroxy FA, i.e cardiolipins, in view of their polar groups being present at the lipid /water junction of phospholipid head groups (fig3 as well as 4c). Secondary to this, an indirect redox mode could get modulated via the redox manipulation of a specific lipid constituent first, following that would stimulate the iPLA2γ action. Once this mode is present, besides hydroperoxy FA, hydroxy FA in addition to any other acyl chains that stimulates the irregularities along with structural changes within the lipid bilayers have the capacity for activation of the enzyme.

In a complicated cellular surroundings, H2O2 could start non- enzymatic lipid peroxidation through the Fenton response (that produces hydroxyl radical having the ability of starting lipid peroxidation) [84], with the following lipid hydroperoxides along with that later obtained reactive electrophiles may liberate the free hydroperoxy FA (hydroxy

FA),that may stimulate its population subsequently. The feasibility of this kind of self-activation is dependent on the experiments of Jaburek *et al*. [40], with the recombinant iPLA2γ was observed to hydrolyze oxidized cardiolipin, particularly liberation of 9- hydroxyl-octadecenoic acid [44].

4. Relianceon Lipid Bilayer Structure along with Cardiolipin 4.1Cardiolipin in addition to iPLA2γ

Cardiolipin,1,3-bis(sn-3'- phosphatidyl) sn-glycerol, is a distinctive class of lipids, having classically one,but clearly 2 negative charges, within a small head group with classically 4 hydrocarbon tails. Two phosphatidic acid components that connect with a glycerol backbone in the centre, thus generating a dimeric structure. At pH about7, just a single phosphate is ionized, that lets Cardiolipin to trap protons within its head group along with hence locate the proton pool close to the surface of the inner membrane. The tiny head group possessing 4 hydrocarbon tails results in lipid bilayers getting destabilized via negative curve stress [85].

The final step in generation of Cardiolipin continues in the matrix side of the, inner mitochondrial membrane, when cytidine di phosphate, diacyl glycerol (CDP-DAG), a construct of CDP-DAG synthase (from phosphatidic acid, along with CTP as precursors) gets changed to phosphatidyl glycerol(PG). Following PG as well as CDP-DAG, liquefaction by Cardiolipin synthase generates cardiolipin [86]. Cardiolipin transacylation is further modulated by the particular transacylase tafazzin (TAZ) residing in the outer inter membrane among OMM as well as IBM. Before this, the initial budding generated cardiolipin located in the inner or matrix, lipid leaflet of IBM needs to turnover towards the outer lipid leaflet.The prior reasoning that iPLA2γ takes part in this remodeling of cardiolipin via deacylation got queried subsequently [87].

Other than other cellular membranes, mitochondrial membrane totally (possesses) around 22%of cardiolipin, besides 37% of phosphatidylcholine (PChol), 31%of phosphatidylethanolamine, as well as 6% phosphatidylinodsitol (PI) [88]. IMM possesses 20%of cardiolipin,that has greater amount in the crista junctions at the place of OMM as well as IMM coming intricately to the crista outlets, while yeast OMM possesses just 4% of cardiolipin [86]. The acyl chains are tissue particular.Human heart possesses majorly cardiolipin,linoleoyl (C18:2), in addition to cardiolipin with alllinoleoyl(C18:2), tails[89].In the mouse brain, cardiolipins with$(C18:1)_4$, $(C18:1)_3$-(C20:4), as well as $(C18:1)_3$-(C22:6) acyl chains prevailed [108].The mitochondrial isoforms of nucleoside-di phosphate kinase D(NDPKD) is located in the outer inter membrane space,in the layer among OMM as well as IMM.Then NDPKD translocates cardiolipin among OMM as well as IMM, yielding the signal for mitophagy [77, 91] amount Cardiolipin is necessary for the mitochondrial cristae architecture [92]. Like the optical atrophy 1 (OPA1) protein guarantees the fusion of both OMM as well as IMM along with generates a ''bottle cork'' for cristae outlet. A smaller type of OPA1(s-OPA1) removed from the long L-OPA1 via protease OMA1 crosstalks with cardiolipin, that is necessary for right cristae morphology as well as IMM fusion [93]. Akin to that Complex I [94], Complex IV [95], as well as ANT need to touch cardiolipin for adequate working, in addition to F_O constituent of the ATP- synthase [97]. The cristae outlet get embraced by crista junctions where OMM as well as IMM reciprocally crosstalk (figure2). These contacts get guaranteed by protein complexes namely MICOS join with the SAM complexes of OMM [98], along with by the particular structure of cardiolipin.

Hydrolysis of tetraoleoyl (C18:1)-cardiolipin by iPLA2β resulted in the liberation of monolyso cardiolipin as well as a di lyso cardiolipin [99]. No PLA2 action was detected towards di lyso cardiolipin. As compared to that, cardiolipin hampered iPLA2 activity for other phospholipids.Other studies observation was that particularly 9- hydroxyl-octadecenoic acid was seen on the iPLA2γ modulated hydrolysis of oxidized cardiolipin [44].

5. Fattyacids modulatesignaling by iPLA2γ 5.1 mitochondrial FA's in role of messengers in signaling of particulars

As suggested earlier, FA's act as the intra mitochondrial Messengers in addition to starters of mild uncoupling causing an antioxidant effect. Association among FA β oxidation in addition to the simultaneous escalated superoxide generation that is subsequently correlated with the activation of iPLA2γ have been observed in a lot of tissues that are heart, along with skeletal muscle. The ideal example is the FA's-activated insulin liberation (FASIS) in pancreatic β cells. In this case apart from a supposed direct redox sensitive insulin liberation, G- protein coupled receptor (GPR40) gets amplified is yielded by the intra mitochondrial redox signaling. This gets manifested by H2O2 caused from ETFQAOR-generated Superoxide. H2O2 results in direct activation of iPLA2γ, that later removes Fatty acids from phospholipids that are components of the mitochondrial membrane. The FA's that have got cleaved move to the plasma membrane, where they further activate the GPR40 pathway of FASIS [21]. This exaggeration is responsible for about60% of FASIS-produced insulin.

5.2. Mitochondrial Lyso phospholipids in role of Messengers in signaling of Particulars

Although deep information on phospholipids as well as cardiolipin generation along with transport of phospholipids among endoplasmic reticulum (ER) in addition to mitochondrial membrane, no agreement exists about if mitochondrial phospholipids get remodeled by mitochondrial acyltranferases like glycerol-3 phosphate acyltranferase 1 as well as 2(GPAT1, 2) isoforms residing on OMM as well as if Lysophospholipids get translocated back to ER for reesterification [100].

One can posit that the redox manifested cleavage of the mitochondrial phospholipids by iPLA2γ catalytic action might further be concomitantly escalate the H^+ leak of the IMM. Nevertheless, this has not been seen.The total need of the iPLA2γ –based H^+ transportation getting manifested either via ANT 1 or UCP2, pointed that the iPLA2γ catalytic action is under tough control.In the studies where utilization of recombinant iPLA2γ whose reconstitution in phospholipid vesicles verify the reversible direct activation of the enzyme by H2O2, pointing to a reversible oxidative manipulation of protein thiol(s).

5.3. Hydroperoxy FA, Hydroxy FA, as well as other Lipid Peroxidation Components - Messengers in Signaling of Particulars

Ideal citation of signaling of peroxidized products of cardiolipin bothers the starting of mitochondrial- based cell demise, apoptosis. The uniform agreement was that Lipid

peroxidation of cardiolipin in addition to later transport of cardiolipin oxydeveloped components to the OMM represented a signaling point of '' for start of no return''of apoptosis [81]. Supposedly OPA1 trimers in the cristae outlets get discontinued in these early phases of apoptotic start [101] as well as let 2-dimensional fusion of the intra cristal membrane cardiolipin to IBM as well as the later above detailed reresiding to OMM.All these alterations cause a liberation of cytochrome c from the mitochondria to cytosol, starting mitochondria-based apoptosis.

6. Physiological cytoshielding as well as Controlling Parts of iPLA2γ

6.1 Mitochondrial iPLA2γ in heart Physiolog as well as Pathology

Heart failure(HF) is correlated with FA extraload along with Oxidative stress from the collection of cardiotoxic lipid constituents as well as oxidized fatty acids metabolites, that are eicosanoids, docosanoids as well as linoleic metabolites [35, 102], in addition to a fast enhancement In action of some Mitochondrial iPLA2γ [103]. Pharmacological hampering of iPLA2 action was observed to ameliorate mitochondrial phospholipids deletion as well as avoid myocardial ischaemia /reperfusion damage [104]. The particular part of iPLA2γ In heart was determined by utilization of cardiac myocyte-particular iPLA2γ KO(CMiPLA2γ KO)mice. Hearts of CMiPLA2γ KO mice showed normal haemodynamic function, standard glycerophospholipid constitution as well as unaltered rates of mitochondrial respiration in addition to ATP generation, yet ameliorated Ca^{2+} -stimulated permeability transition pore (mPTP) opening [105].

In a following study Moon etal., illustrated that heart failure stimulates particular myocardial mitochondrial phospholipases, which escalated Ca^{2+} -based generation of toxic hydroxyl-eicosatetraenoic acids(HETEs).The activation of phospholipases got mitigated so that a significant facilitation got stimulated for the generation of shielding epoxy eicosatetraenoic acids(EETs)[29].Mode of action of HETEs is the Ca^{2+} -stimulated opening of the Mitochondrial permeability transition pore (mPTP) in the myocardium that is undergoing failure, as well as the selective pharmacological blocking of either iPLA2γ or lipoxygeneases mitigated mPTP)opening in these failing hearts. Intriguingly, the main Mitochondrial phospholipase implicated in Ca^{2+} -stimulated liberation of arachidonic acid in mitochondria from non-failing heart was isolated as the cytosolic phospholipase A2ζ (cPLA2ζ) alias Calcium dependent phospholipase A2ζ in the particular article).The cPLA2ζ is then attributed the shielding EET generation in the healthy hearts as well as iPLA2γ generating HETEs in mitochondria from hearts at the verge of failure [29].

As compared to the discovery of iPLA2γ possessing a necessary mode of action aid to mPTP along with cardiac myocyte necrosis/ apoptosis, the iPLA2γmight also be a necessary physiological controlling cellular redox status, a mitochondrial iPLA2 has further been pointed to possess a part in the progression of cardio shielding signal [106]. Selective Pharmacological blockade of mitochondrial iPLA2(s) interferes the redox-based activation of mitochondrial protein kinase C_{ε} followed by opening of ATP-sensitive K^{+} channel [106]. The results pointed that a spatitemporal liberation of Hydroperoxy FA by mitochondrial iPLA2 results in progression of redox cellular signaling at the time of cardioshielding. Nevertheless, greater studies in detail are missing, as well as different potential parts of iPLA2γ in heart still not fully unveiled.

6.2. Role of Mitochondrial iPLA2γ in Brain Physiology as well as Pathology

In the CNS, phospholipase A2 has been known for long to develop Signals by lipid 2nd messengers that are essential for key neuronal working, that are neurotransmitter liberation, long term potentiation, as well as cognitive working [107]. PLA2 activation in cerebral ischemia has got associated with escalated lipid peroxidation [108], as well as iPLA2γ was the major phospholipase action existing in rat hippocampus [107]. Later studies with the utilization of iPLA2γ KO observed an obligatory part of iPLA2γ in neuronal mitochondrial structure along with working [109]. Furthermore iPLA2γ KO mice possess the properties of significant alterations in the hippocampal lipids, that are cardiolipin amount as well as molecular species constituents, the existence of the enhanced amounts of oxidized lipid molecular species. Additionally, the iPLA2γ KO mice documented significantly escalated heteromorphic structures that are specifically highlighted in the hippocampus. The identification of escalated structureslabeled them as degenerating mitochondria [109]. The outcomes derived from iPLA2γ KO mice further stressed on the varied biochemical in addition to neuro pathological aberrations occurring secondary to iPLA2γ loss of working that included disturbance in the iPLA2γ modulation of signaling in addition to membrane lipids refashioning, degeneration of mitochondria, escalated Oxidative stress, along with neurological Impairment getting apparent [109],

The part of iPLA2γ in the controlling of mitochondrial lipid peroxidation along with mitochondrial Impairment was evaluated by utilization of rotenone stimulated rat model of parkinson's disease. In vivo, along with in vitro experiment documented that iPLA2γpossesses a key role in sustenance of classical mitochondrial working. Reduction in iPLA2γ action escalated lipid Oxidative stress that was correlated with mitochondrial disorders [110]. Hence neuro egeneration has a robust association with iPLA2γ action,as well as when this activity is interfered with,then up regulation of the iPLA2γ action can restore both mitochondrial membrane along with its working.

Additionally, iPLA2γ action in the brain was illustrated via quantitative evaluation of peroxidation along with hydrolysis of mitochondrial cardiolipins with utilization ofglobal (phosphor) lipidomics along with redox lipidomic for demonstration as well as identification of cardiolipin modifications at the time of regulation of the cortical impact [111]. On contrasting the in vivo, along with in vitro outcomes with genetic manipulations along withmain cardiolipin enzyme for metabolism of iPLA2γ as well as tafazzin,it was demonstrated, that the cardiolipin oxidization as well as hydrolysis of cardiolipin work in the form of reciprocally symbiotically escalating constituents of the etiopathogenic mode of mitochondrial injury in case of traumatic brain injury [111].

Furthermore current ongoing work on the antioxidant part of iPLA2γ in the brain mitochondria separated from WT as well as iPLA2γ-KOmice corroborates antioxidant part of iPLA2γ in the brain,with the use of a mode iPLA2γ-based,ANT modulated, amelioration of mitochondrial superoxide generation by mild uncoupling [85].

6.3 Role of Mitochondrial iPLA2γ in BAT Physiology as well as Pathology

Brown adipose tissue (BAT) as well as,brown in white(brite) adipose tissue further known as beige AT,are the main areas of mammalian nonshivering thermogenesis, besides mitochondrial UCP1, particularly for these tissues is the critical feature for heat generation(rev in ref 112,rev byus in ref 1,2).Since UCP1 working is necessarily based on free fatty acids(FFA) in the mitochondria, the invention of N-terminal mitochondrial residing Signal of iPLA2γ readily point that iPLA2γ working might be attached to the UCP working in addition to that iPLA2γ might aid in respiration as well as thermogenesis in BAT mitochondria [26]. Agreeing with this posit, the iPLA2γ-KOmice reveal significantly decreased cold tolerance, despite the UCP mRNA expression escalated a little bit following cold getting induced, that might imply a compensatory mode to manage with changed heat production [114].

The initial evaluation deeply of in vivo BAT Metabolism of oxidants on acute activation of thermogenesis gets parallel to the escalated amounts of mitochondrial superoxide, H2O2 as well as lipid hydroperoxides [115]. Furthermore, the escalated generation of mitochondrial oxidants runs adjacent to switch in a Cysteine thiol redox status along with results in sulfenylation of UCP1 Cys 253 [115]. Since these observations, a recent posit was made by Jaburek et al. [23] that the escalated amounts of oxidants result in activation of redox sensitive mitochondrial phospholipase iPLA2γ,that further yields budding fatty acids for the UCP1- modulated uncoupling, hence verifying heat generation [112]. However, the particular part of FA's along with lysophospholipids secondary to enzymatic action of the mitochondrial phospholipase iPLA2γ in BAT mitochondria are still to be unraveled.

7. Conclusion

Inspite of robust work by a lot of laboratories for finding the physiological along with pathophysiological part of phospholipases having an action in or on mitochondria, our insight of the degree of phospholipases taking part in the controlling of mitochondrial as well as cellular functions continue to be infinite. In this review our concentration was on getting the molecular modes of anti-oxidant synergistic actions implicating phospholipase iPLA2γ as well as selective fatty acids that result in translocation of mitochondrial SLC 25 family proteins.

The individual capacity of iPLA2γ to detach phospholipid acyl chains from sn1 as well as sn2 positions lets different methods of the spatiotemporal liberation of saturated along with poly unsaturated FAs(PUFA)of characteristics. The situations under which the specific liberated FAs can work as controllers of mitochondrial H^+ backflow into the matrix of the mitochondria as well as later as controllers of mitochondrial superoxide generators were detailed. Additionally, the phospholipid constituents of the inner mitochondrial membrane that was decided by the lone amount of cardiolipin, lets iPLA2γ to liberate particular lipid species, that might later work as an individual- mitochondrial obtained modulators of cellular signaling.

A redox –based controlling of iPLA2γ has got isolated in the form of a significant crucial parameters needed for the working as well as anti-oxidant action of iPLA2γ.Despite some advances have been achieved in explanation of the molecular mode of redox activation of iPLA2γ,still plenty of queries need an answer. These are isolating the molecular species implicated in the activation of iPLA2γ, along with delineation of the particular amino acid residues of iPLA2, that undergo oxidative post-translational modifications. A deep information of the molecular mode implicated in the controlling of iPLA2γ will aid in getting insight as well as anticipate the still unraveled cytoshielding as well as controlling part of mitochondrial iPLA2γ in relation to cellular physiology along with pathophysiology.

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