IJPSR (2021), Volume 12, Issue 3 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 March 2020; received in revised form, 19 June 2020; accepted, 28 June 2020; published 01 March 2021

ONGOING ADVANCEMENT IN THE COMPREHENSION OF MITOCHONDRIAL PROGRESSION WITH AN EXCEPTIONAL SPOTLIGHT ON ITS RELATIONSHIP WITH CANCER AND POSSIBLE THERAPEUTIC STRATEGY

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Keywords:

Mitochondria cancer, Mitochondrial fission, Mitochondrial fusion, Natural compounds, Quercetin, Aloe-emodin, Berberine, Resveratrol

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ABSTRACT: Cancer is one of the main reasons of death around the world and the quantity of new incidents keeps on rising. Despite ongoing advances in conclusion and remedial systems, many malignancy-related passes happen, demonstrating the requirement for better treatments and symptomatic methodologies. Mitochondrial morphology is dependent on continuous fusion and fission strategies that are essential for monitoring a normal mitochondrial function. Past years major discoveries have indicated that the characterization of fission and fusion is a little machinery, which is known as the physiological role of mitochondrial dynamics. Mitochondria (MND) and metabolic adjustments have been perceived as critical for growth movement. The numerous components of those organelles square measure in person connected to their morphology. Late confirmation proposes a significant association between mitochondrial (MNDL) construction and ill health, together with neurodegenerative, incendiary ailments and malignancy. Here, we scrutinize present-day movements within the perception of mitochondrial gestures with a special target with its liaison to cancer and therapeutic ways *via* synthetic and natural bioactive actives. Some notable compounds in the above class are Curcumin, Mahanine, aloe-emodin, Dioscin, Dantron, Flavo-pridiol, Xantho-humol, resveratrol, and quercetin.

INTRODUCTION: Mitochondria (MND) are double membranous organelles in which the inner membrane is larger than the outer one. For this reason, the inner membrane of the MND folds within, forming a special figure known as cristae. The inner MND membrane (IMM) contains the subunits for organic processes [1,] and this inner MNDL membrane is coated by a second membrane known as the outer MNDL membrane (OMM) [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(3).1421-32

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(3).1421-32

We tend to know the MND as the 'Powerhouse of the Cell because not only they generate adenosine triphosphate (ATP) *via* organic processes [3], but additionally participate in varied synthesis pathways (PWS) such as pyrimidine and purine biogenesis, haematin biogenesis [4] the management of N_2 equivalence in organic compounds revolution, gluconeogenesis, organic compound generation, and carboxylic acid degeneration and prolongation [5].

They additionally participate in cell signaling *via* control of the protein-protein interaction or by controlling the cellular concentration of metal ion (Ca^{2+}) and reactive atomic number 8 species [6]. Throughout numerous biological diseases, MNDL morphology is altered, as in the case as once there

is a lack of nutrients in our body MND mix along to share their nutrient and additionally their polymer, ETC elements to take care of their OXPHOS [7]. However, just in the case of the high energy demand of a district of body MND bear division or known as fission as a result of the move apace than lager one [8].

Fission additionally occurs in the mitotic cell to share an equal quantity of MND to the female offspring cells [9]. Several queries arise in the matter of MNDL dynamics; however, here we are going to reach answering a most uncertain question- Does MNDL dynamics play any role in the tumorigenic process. Does any oncogenic signaling play a crucial role in the morphological alteration of MND.

Mitochondrial Dynamics: In past years, it is considered that MND is an unbending structure. However, since mitochondria (MND) are recognised as organelles that, latter cell division, move through the cells, combine and experience autophagy or mitophagy throughout their direction. In cancer cells (Crc) as well as in typical cells, MND experiences division, and combination. The enormous capacity of MND is personally connected to their morphology, and there is a delightful harmony between the combination and splitting, which control the mitochondrial (MNDL) legitimate capacity [10].

Uncontrolled parting prompts broad MNDL fracture, which impacts the ordinary metabolic capacity of our body. On the other hand, the ceaseless combination brings about the hyper melded organization, which neutralizes metabolic abuse, jams cell uprightness, and secures against autophagy.

In ordinary cells, MNDL combination and parting are adjusted to meet cell metabolic requests and manage the expulsion of harmed organelles [11]. Modification in combination and splitting experiences change in the status of well-being and malady [12].

Some guanosine triphosphates (GTPase) direct MNDL flow. External MNDL film (OMM) combination is managed by mitofusin-1 and mitofusin-2 (mfn1 and mfn2), and the combination of internal MNDL layer (IMM) is controlled by optic decay 1 (OPA1). Also, the splitting of MND is managed by unique related protein 1 (DRP1).

Mitofusins Post Translational Modifications: AnN-terminal kinase (JNK) interceded phosphor-rylation of Mfn 2 at ser 27 brings about the enrolment of the E3 ubiquitin ligase Huwe 1 and possible debasement of Mfn 2 [13].

Acetylation / Ubiquitination: Acetylation of Mfn1 at lys491 initiates the MND Llimited ubiquitin ligase March 5, prompting ubiquitination and debasement of Mfn1 (Shaw and Nunnari, 2002). March 5 is additionally debased Mfn1 amid the M-period of the cell cycle where the MNDL arrange is should have been divided to enable equivalent dissemination of MND to the little girl cells [14].

Opa1 Proteolytic Processing: The elective joining of OPA1 mRNA produces eight individual transcript variations, which are handled by the lattice ATPase (m-AAA) protease paraplegin and the inward film ATPase (I-AAA) protease Yme1L, yielding long (L-OPA1) and short (S-OPA1) is forms, separately.

Proteolysis of OPA1 is controlled by changes in the electrochemical and proton angle over the IMM, while a combination of IMM and renovating of cristae requires both L-OPA1 and S-OPA1, in this, manner connecting MNDL morphology with lively state [15-16].

Drp1 Post-translational Modifications: Supplement hardship causes cyclic AMP-subordinate kinase A (PKA) - intervened DRP1 phosphorylation (PPL) at ser 637, coming about DRP1 hindrance. Subsequently, the MNDL organizes wire to share metabolites and keep up ATP generation.

Calcineurin dephosphorylates DRP1 ser 637, bringing about DRP1 enactment and a parting of MND organize. Amid mitosis, Ral-restricting protein 1 associates with CDK1 and fills in as a framework protein that takes into account CDK-1 intervened PPL of DRP1 at ser 616. Oncogenic MAPK flagging phosphorylates DRP1 ser 616 through direct ERK-DRP1 communications [17].

Sumoylation (SUMO): Over articulation of E3 SUMO, MND tied down protein ligase (MAPL) sumoylates DRP1 and increment MNDL splitting.

What's more, the SUMO protease SENP5 de-sumoylates DRP1 amid the G2/M period of the cell cycle and furthermore brings about mitochondrial discontinuity. This opposing outcome might be because of various sumoylation locales on DRP1 **Fig. 1.**

Nitrosylation: NO creation is accounted for to cause S-nitrosylation at DRP1 cys644, which improves DRP1 GTPase movement and MNDL parting. Another report proposes that while S-nitrosylation of DRP1 has been seen in mind tissue from Alzheimer's patients [18].

Ubiquitination (Ub): The E3 ubiquitin ligase PARKIN specifically targets and poly-ubiquitylates DRP1 bringing about proteasomal-interceded DRP1 corruption and MNDL combination. Then again, March 5 ubiquitylates DRP1 and elevates enrolment of DRP1 to the OMM, and expanded MNDL parting [19].

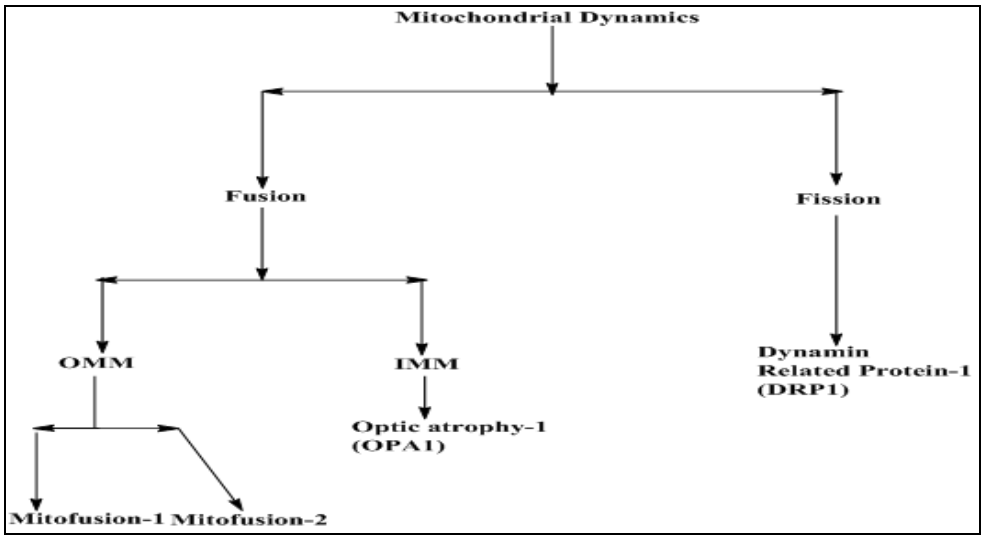


FIG. 1: MITOCHONDRIAL DYNAMICS REGULATORY PROTEIN

Molecular Mechanism of Shaping Mitochondria: MNDL form is organized with the aid of a family of GTPase with structural impartiality to progressive proteins elaborated in advance. Mitofusins are the GTPase that are necessary for OMM fusion, and they may be controlled *via* ubiquitination and PPL. The E3-ubiquitin ligase PARKIN impresses both MFN1 and MFN2 with ubiquitin (Ub), adjusting pastime and ranges. However, the de-ubiquitination through USP30 counteracts PARKIN MNDL coalescence. PINK1, the kinase is capable of phosphorylating ubiquitin sequence on OMM proteins together with MFN2, can then noviciate PARKIN. PPL of MFN2 using JNK in reaction to mobile stress alerts the new coming of the E3-ubiquitin ligase HUWE1, prompts MFN2 deterioration by way of the proteasome [20]. Additionally, miR-a a hundred and forty, which can be induced with the aid of decomposition or genotoxic insults, negatively adjust MFN1 transcription. The transcriptional co-activator PGC-1-β has been recommended to modify MNDL integration through Mfn2 and other MNDL genes like OPA1. Mito PLD, a unit of the phospholipase D family, is attached to the outer membrane and transforms cardiolipin to phosphatidic acid. These synergistic activities are needed for mitochondrial fusion. In mammalian cells, the indispensable member of MNDL fission is DRP1 which is bestowed with a cytoplasmic restriction (inactive shape). It unpredictably unites with OMM at the network of MNDL partition, in which the fission happens advantageously at ER-contact regions. DRP1 is troublesome to plenty of post-translational alterations in feelings to cellular catchword. PPL of DRP1 at Ser637 produces the signal that maintains protein transformation from the MND to the cytoplasm. Perusing MNDL depolarization, upward thrust in cytosolic Ca^{2+} actuates cytosolic Calcineurin (CaN) that dephosphorylates DRP1 on Ser637, bringing about its movement to MT. CaN itself causes its difficulty in translational control with the aid of miR-499 in a p53-structured manner. On the other hand, protein kinase A (PKA), following cyclic AMP exhilaration, phosphorylates this sediment,

leading to the stretching of mitochondria and protection to various seasoned-apoptotic insults. DRP1 positioning to MND is an arrangement requiring connections on the OMM (FIS1, MFF, MiD49, MiD51 and Mcl-1L). The MNDL ubiquitin ligase Mitol / March5 advocates mitochondrial administration in a DRP1- and MiD49-established manner. Furthermore, MITOL/MARCH5 also designs MFN1 and FIS1. The MTL anchored protein ligase (MAPL) encourages sumoylation of DRP1, focussing on MND and expediting MNDL fission. Sumoylation may be inverted by utilizing the SUMO protease SENP5. For the duration of mitosis, CDK1/cyclin B phosphorylates DRP1 at Ser616 to set off mitochondrial fission and right organelle segregation. ERK2 can also phospho-rylate DRP1 at Ser616 at some point of MAPK-mediated reconstruction. Imposed expression of MTP18 coordinates the recruitment of DRP1 to mitochondria. DRP1 also can be S-nitrosylated at Cys644 in reaction to a crash in NO promoting MNDL partition. Ultimately, the interplay of DRP1 with phosphatidic acid (PA) restricts DRP1 fission exercises and variates the security towards MNDL fusion. OPA1 is muddled in inner membrane refinement. Alternative splicing of OPA1 gives upward drive towards long bureaucracy (L-OPA), which can be proteolytically split paperwork (S-OPA) by using internal membrane peptidases, OMA1 and YME1L. As L-OPA1 induces MNDL fusion, uncontrolled aggregation of S-OPA1 can either induce or hike MNDL fusion or fission respectively and stimulate MNDL disintegration. The IMM peptidase YME1L essentially breaks OPA1 at the S2 website addressing MNDL fusion. However, OMA1 cleaves OPA1 at the S1 website constitutively or in reaction to pressure, activating MNDL fragmentation. The expression of OPA1 is under evidence-based control of the NF-κB transcription issue, which provides diverse factors for the cellular department and metabolic rearrangement [21].

Cancer Cell Metabolism: Quickly dividing Crc cells require mainly 3 metabolic adaptations: (1) ATP production is increased to maintain high energy demand (2) Macromolecule biosynthesis also increased. (3) Redox state is maintained properly. Crc cells undergo metabolic adaptations. Glycolysis is increased in the environment where a sufficient amount of oxygen is present, but normally it increased in anaerobic conditions. This phenomenon is called aerobic glycolysis or also called the "Warburg effect". Lactate produced by aerobic glycolysis and low rate of oxidative phosphorylation is one of the most common alterations in tumour microenvironment [22].

Metabolic Responses of Oncogenes and Tumour Annihilator: Different oncogenic and tumour suppressive PWS adding to Warburg impact like PI3K PWS and Pyruvate kinase M2 (PKM2) PWS, *etc*. The initiated rate of oxygen-consuming glycolysis which is normal for the Warburg impact, is driven by sub-atomic exercises that likewise advance cell change. These are countered by other sub-atomic exercises that smother change. The commitment of development factor receptors fortifies phosphatidylinositol-3-phosphate kinase (PI3K), which initiates Akt1. What's more, the initiated Akt1 at that point up-controls glycolysis and incite mTOR while inactivating forkhead box subfamily O (FOXO). Without FOXOs, inter-pretation of elements that for the most part repress glycolysis and control receptive oxygen species (ROS) is blocked, mTOR enactment fortifies interpretation of development-related proteins, for example, Myc and builds hypoxia-inducible factor (HIF) transcriptional action. HIF1 partners with PKM2 to drive proglycolytic quality articulation. PKM2 is a then again joined type of pyruvate kinase (PK or PKM1) and is communicated at abnormal states in disease cells. The expanded level of Myc fortifies PKM2 age and PKM2 acts to moderate glycolysis. Glycolytic intermediates are occupied by the pentose phosphate pathway (PPP), which supports nucleotide union and creates NADPH. HIF1 enactment likewise prompts up the direction of glucose transporters, glycolytic catalysts and pyruvate dehydrogenase kinase (PDK), which hinders the section of pyruvate into the tricarboxylic corrosive (TCA) cycle through pyruvate dehydrogenase (PDH). PDK articulation is additionally expanded by OCT1 transcriptional action. The creation of LDH is expanded attributable to expanded pyruvate generation from glycolysis, and lactate at that point is exchanged to the tumor microenvironment with the assistance of monocarboxylate transporters (MCT). Tumor cell adjustments amid digestion are controlled by tumour silencers, for example, p53, phosphatase and PTEN (tensin homolog erased from chromo-

some 10), AMP-subordinate kinase (AMPK), TP53 -incited glycolysis and APS controller (TIGAR), FOXOs, and a combination of cytochrome C oxidase 2 (SCO2). PTEN down-manages the PI3K pathway, AMPK represses mTOR, TIGAR squares glycolysis, FOXOs control an anti-oxidative reaction, in this manner expanding ROS rummaging, and the p53 target, SCO2, directs cytochrome c levels and improves MNDL oxidative PPL. The articulation of every one of these controllers is driven by p53 and, additionally, FOXO. Loss of these tumour silencers in this way brings about constitutive initiation of development advancing systems and emphatically inclines cells to change [23] **Fig. 2.**

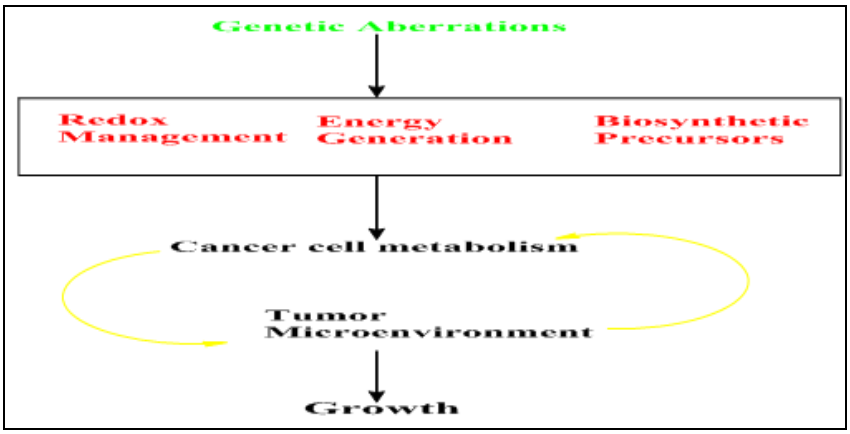


FIG. 2: CANCER CELL METABOLIC ADAPTATIONS

Metabolic Flexibility of Crc: Warburg impact is favorable for the development of malignancy cells; however, there are some Crc that is not emphatically glycolytic. If fundamental, this sort of tumour cells utilizes unsaturated fats, lactate, and amino acids as an elective wellspring of vitality. The event of irregular articulation in tumour cells of carnitine palmitoyltransferase-1C (CPT1-C). CPT1 protein direct beta-oxidation of unsaturated fats. CPT1C is, for the most part, introducing in mind, and it is like CPT1A and CPT1B both have a similar impact; they catalyze the build-up of L-carnitine either acyl-CoA in the OMM. Some trial confirmations when mice have a low level of CPT1C it ends up stout when a high-fat eating routine is provided. It experiences insulin opposition and more inclined to non-alcoholic greasy liver illness [24]. What's more, when CPT1A level is high, it prompts microcephaly and shapes long-chain unsaturated fats in the cerebrum. CPT1C is controlled by AMPK, actuation of AMPK prompts up the direction of CPT1C, and it empowers FA oxidation [25]. AMPK and p53 is confined in the CPT1C promoter and prompts H2B PPL and increment CPT1C interpretation [26].

Regulation of MND Dynamics *via* Oncogenic Signal: Cancer is a group of disease; as we don't know the actual cause of cancer, several studies have revealed that over activation of oncogenic signalling leads to remodelling MND and its metabolism is associated with decreased OXPHOS, ATP production, increased ROS and glycolytic efflux [27]. MNDL morphological changes occur due to different states of energy demand, and oncological signalling control the metabolic rate of Crc. Here some examples of alteration in metabolism and MNDL shape-Primary fibroblast display fused MND and relay on OXPHO. In contrast, B-RAF-driven melanoma cells contain fragmented MND and increased metabolism [28]. There are mainly three signalling pathways that are involved in MNDL dynamics and Cancer- (a) Oncogenic MAPK signalling,(b) PI3K-Akt signalling, (c) Myc overexpression [29].

Oncogenic MAPK Signalling: MAPK signalling is mediated by a variety of growth factors, such as platelet-derived growth factors (PDGF) and epidermal growth factors (EGF). It is one type of receptor tyrosine kinase-mediated signalling PWS, and this mitogen-activated protein kinase (MAPK) PWS is frequently mutated in cancer cells [30]. For this reason, researchers use RTK inhibitors but they quickly acquire resistance to this drug. This is a well-understood signalling PWS which over expressed in Cancer [31]. In this signalling, most of the mutation occurs in the GTPase protein called

Ras followed by RAF (rapidly accelerated fibro sarcoma), MEK (mitogen-activated protein kinase) and ERK (extracellular signalling regulated kinase) [32] **Fig. 3**.

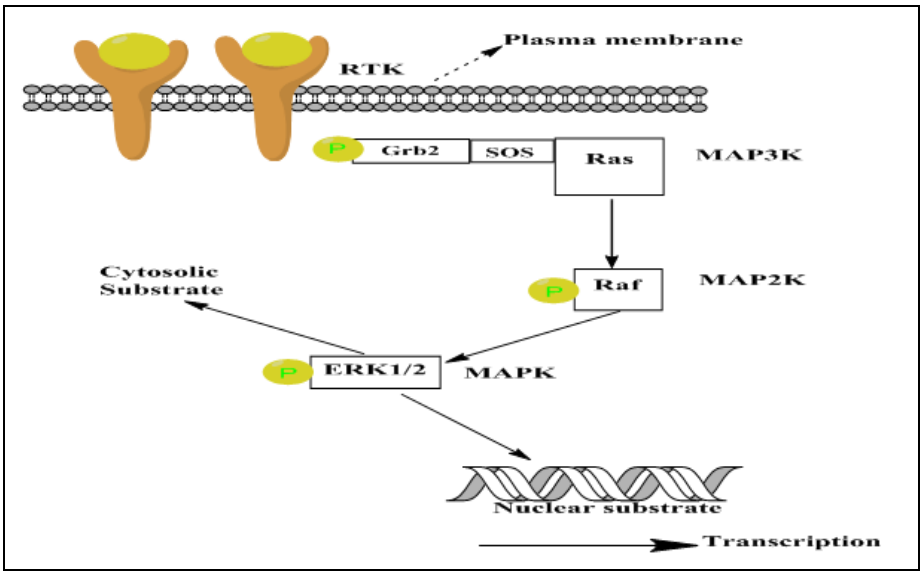


FIG. 3: MAPK SIGNALLING PATHWAY

Earlier it was determined that DRP1 is an ERK substrate and PPL of DRP1 by ERK leads to MNDL fragmentation, and it can proceed through MAPK PWS. But further research works reveal that it depends on the site of PPL.

PPL of DRP1 at Ser616 by ERK leads to MNDL fission. In some cases where Raf and Ras are mutant, the metabolic shift occurs towards OXPHOS, and d increase MNDL biogenesis by up-regulating melanocytic specific transcription factor (MITF), which increases the production of transcriptional co-activator peroxisome proliferator activator receptor gamma coactivator-1 alpha (PGC-1α).

DRP1 is an important mediator of MAPK induced tumorigenesis across multiple stages, highlighting two impacts of DRP1 (1) Metabolic reprogramming during transformation and (2) Requirement for equal MNDL distribution in rapidly proliferating cells [33].

PI3K-Akt Signalling: The Ser / Thr kinase Akt, also known as protein kinase B or PKB, has criticala role in regulating diverse cellular functions, including metabolism, growth, proliferation, survival, transcription, and protein synthesis. This signalling PWS is activated by various substrates like-RTKs, interim's, B and T-cell receptors, cytokine receptors, G protein-coupled receptors, and others that stimulate the production of PIP3 by phosphoinositide 3-kinase (PI3K)[34]. Hyperactivation of PI3K signalling occurs in many Crc with somatic mutation or loss of epigenetic silencing of the PI3K inhibitor PTEN.

This type of alteration occurs in nearly 40% of cancer cells. Over-activated PI3K Akt signalling leads to increased glucose uptake by the Crc, which is similar to Ras-driven Crc, suggesting that PI3K-Akt signalizing fragments the MND. Nutriment and oxygen insufficiency are prime consequences of Crc propagation.

To conquer this difficulty, Crc turnsover on PI3K-Akt signalling to boost autophagy, a self-subsistent system that capacitates the cells to use insignificant macromolecules as anorigin of power. When growth signals are elevated in surroundings, it triggers mTORC1 *via* Akt to promote protein, lipid, and nucleic acid synthesis while inhibiting autophagy.

On the other hand, mTORC1 has been inhibited by7 nutrient and oxygen deprivation, and the energy sensor AMPK (adenosine monophosphate-activated protein kinase which is activated by a high AMP/ATP ratio. Inhibition of mTORC1 allows the cells to maintain the critical concentration of energy and macromolecules proliferation and survival [35] **Fig. 4.**

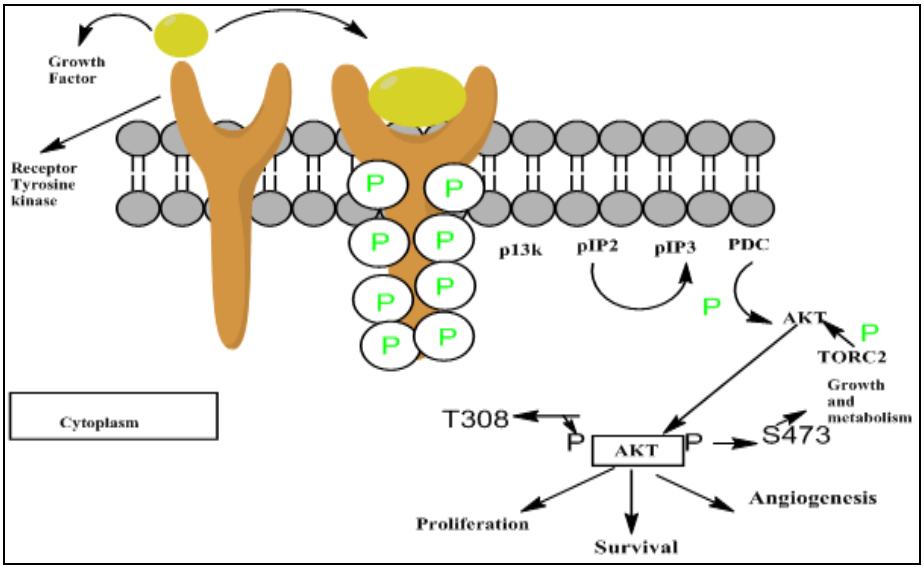


FIG. 4: PI3K-AKT SIGNALLING

MYC Over-expression: Aproto-oncogene Myc encodes a nuclear phosphoprotein that plays a role in cell cycle progression, cellular transformation, and apoptosis. It also regulates cell growth, proliferation, and metabolism. MAPK, IP3K-Akt signalling are the upstream regulators o Myc, which is a downstream regulator. Normally MYC expression is regulated by transcription ally and post-transcriptionally by controlling MYC mRNA and protein's half-life. When the upstream regulators are over-expressed this also increases the MYC expression and leads to tumorigenesis [36]. Oncogenic MYC leads to MNDL biogenesis by over expression of PGC-1β. MYC also maintain the MNDL dynamics, MYC knockout MEFs smashes MND, whereas re-expression of MYC stimulates amalgamation of MND. This fusion occurs by up-regulatingOPA1 and mfn2, although DRP1 and FIS1 alignments were also elevated. MYC signalling in triple- negative breast Crc brings about MNDL blending by raising PLD6 (phospholipase D family member 6) [37]. It converts cardiolipin to phosphatidic acid (PA), which is cleaved to triacylglycerol by 1427 phosphatises on OMM [38].

Mtl Dynamics and Cell Cycle: MNDis maintained properly throughout the cell cycle. IntheG1/S phase, MND undergoes fusion to increase energy production and preparation for S phase. MNDL fusion triggers s phase initiation, and this alone is sufficient for G_0 cells to enter S phase and in the case of S, G2, and M phase MND undergo fission. Fragmentation of MND is at the maximum level at mitosis when an equal number of MND is separated in daughter cells. Mitotic MTL disintegration is monitored by kinase engaged in mitosis. It is like aurora a kinase that stimulates Real fixing to MNDL membrane and recruits RalBP1[39]. This RalBP1 leads to cyclin a / cyclin-dependent kinase 1 (cdk1) that phosphorylates DRP1 at ser 616, resulting in MNDL fission [40].

Mndl Dynamics and Cell Death: Apoptosis (APS) is also called programmed cell death, as the cells are programmed to die under some stressed conditions. Crc also face stressful conditions, but they inhibit APS, this is the beauty of Crc [41]. This is a hallmark of Crc. MND plays a crucial role in APS; they secret cytochrome c and other different death-provoking proteins from the inner membrane space (IMS).

Release of this death promoting proteins is a crucial determination point in APS and appears by MNDL outer membrane permeabilization (MOMP). This is controlled by family proteins belonging to B cell lymphoma 2 (Bcl2) [42]. Bcl2 family have both pro and anti- APS proteins [43]. The cooperation between pro and anti-APS proteins is very meaningful and meets with the resolution of whether APS takes place or not [44]. If pro-APS proteins are activated, they lead to cell death via formation of apoptosome [45]. Death signals in the cell triggerpro-apoptotic molecule Bax. Bax combines that leads to the discharge of cyt c from the MNDL inter-membrane area, either by forming pores or by interacting with other MNDL outer membrane proteins [46].

Normally in MND cytochrome c helps in oxidative PPL but outside the MND it induces APS mechanisms [47]. Cytochrome c binds to cytosolic proteins Apaf-1, with cytochrome c attached, the Apaf-1 proteins can assemble into a structure called[48] the apoptosome. Another protein, called caspase-9 (CSP-9), is now triggered up by developing a conglomerate with Apaf-1 in the apoptosome [49]. Caspases (CSP) are proteases that contain cysteine remnant at their active sites and separate whenever aspartic acid remainders are present in their substrate protein [50]. Two type's of CSP show performance in APS: initiator and effector CSP [51]. Initiator CSP, such as CSP-9 is the 1st CSP activated by APS signals. The function of initiator CSP is to activate effector CSP, such as pro-CSP-3 through proteolytic cleavage [52]. CSP-9 cleaves pro -caspase-3, producing active caspase. Caspases (CSP), like other enzymes, act catalytically, allowing a small number of initiator CSP to activate a large number of effector CSP [53]. The accidental activation of CSP could result in apoptosis, but this is prevented by IAPs [54]. Members of Inhibitory APS Proteins interact with CSP and suppress APS by either inhibiting CSP activity or by targeting CSP for degradation [55]. In mammalian cells, the permeabilization of MND by Bax results not only in the release of cyt c but also o IAPs. These inhibitors block the action of IAPs, allowing the cascade beginning with cyt c to activate CSP and culminate in APS. Besides, CSP cleaves nuclear lamina, leading to fragmentation of the nucleus. They cleave cytoskeletal proteins, leading to disruption of the cytoskeleton, cell fragmentation. They also cleave Golgi matrix proteins, leading to fragmentation of the Golgi apparatus [56].

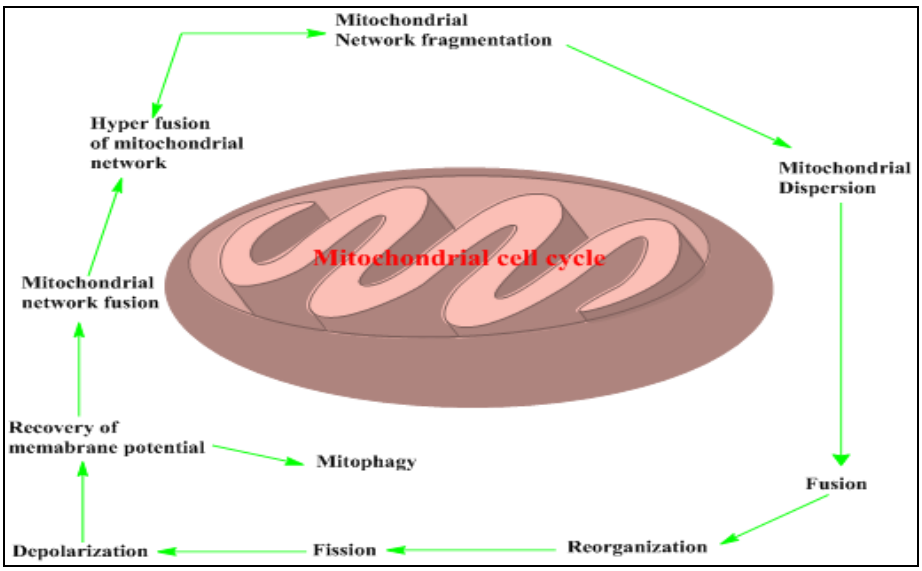
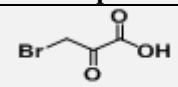
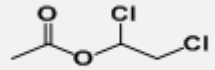
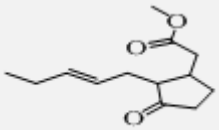
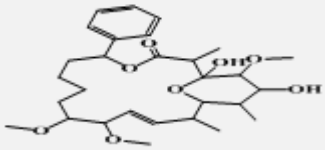
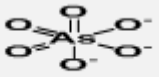
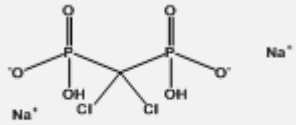
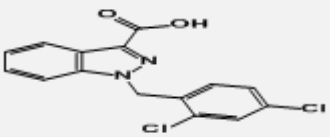
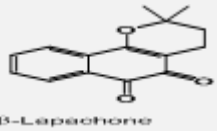
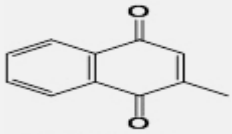
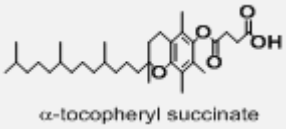
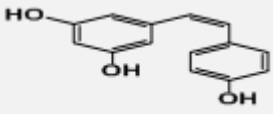


FIG. 5: MITOCHONDRIAL DYNAMIC IN DIFFERENT STAGES OF CELL CYCLE

Targets in Mitochondria to Prevent Cancer: Inhibition of cell death should be an ideal strategy for cancer treatment. Nowadays, drugs are designed to induce cell death of Crc. MND play a crucial role in cell survival-1, it produces energy for survival and it is also a key regulator of the intrinsic PWS of APS. MND controls cell death *via* controllingtheexpression of some pro- APS proteins, it also plays a role in necroptosis [57]. Hreds of evidences that suggest that metabolic alteration affects the Crc to undergo catabolic processes like-APS, necrosis and autophagy. The level of ROS is also an index under the intrinsic pathway of APS. The key objective in the drug discovery deceptions looks for a safe chemotherapeutic agent. The correction of MNDL dysfunctions and the reactivation of cell death can be mediated through pharmacological agents that induce MNDL membrane permeabilization [58]. Bioactive natural compounds contribute a major part in this regard as they agree with these objectives. In the last decades, there were many studies that involved anti-cancer activities of numerous natural compounds where MND dysfunction was specifically targeted. Some notable compounds in the above class are curcumin, mahanine, aloe-emodin, dioscin, dantron, flavopridiol, xantho-humol, resveratrol, quercetin, *etc*.

They perform on diverse integrals of MND either straightly influencing its oxidative PPL and apoptotic signalling or act in a roundabout way by aninflexion of metabolic irregularities cropped up as a consequence of MNDL malfunctions. The details of the compounds and mechanism of action as above are listed in **Table 1** [59-60].

TABLE 1: TARGETING MITOCHONDRIA FOR CANCER THERAPY

Class	Compound	Target and Mode of Action
Metabolic inhibitors	 3-Bromopyruvic acid	HK2-VDAC interaction
	 Dichloroethyl acetate	PDK inhibitor
	 Methyl jasmonate	HK2-VDAC interaction
	 Soraphen A	Acetyl-CoA carboxylase inhibitor
VDAC-targeting and/or ANT-targeting agent	 arsenitetrioxide	ANT ligand, ROS production
	 Clodronate	ANT inhibitor
	 Lonidamine	ANT ligand
ROS regulator	 β-Lapachone	ROS production
	 Menadione	ROS production
Retinoid	All-trans retinoic acid	ANT-ligand
	CD437	Permeability transition pore complex
Natural compounds and derivatives	 α-tocopheryl succinate	Ubiquinone-binding sites -in respiratory complex II
	Betulinic acid	Permeability transition pore complex
	 Resveratrol	F1-ATPase

CONCLUSION: MND is unpredictable organelles that impact malignancy commencement, development, survival, and metastasis, and numerous features of MNDL science past vitality creation effectively add to tumor genesis. These incorporate MNDL masses, flow and cell passing control, redox homeostasis, metabolic direction, and flagging. The interchange between these parts of MNDL science brings about facilitated projects of MNDL control of cell physiology and features the pleiotropic elements of MND in malignancy. Furthermore, like the changing revelations of oncogenic transformations in development factor flagging pathways, transformations in MNDL metabolic proteins are energizing new boondocks in disease biology. The adaptability MNDL offers tumor cells, incorporating adjustments in fuel use, bioenergetics, cell demise defenselessness, and oxidative pressure, take into consideration survival even with antagonistic natural conditions, for example, starvation and amid chemotherapeutic and focused on growth medicines. Hence, to successfully treat growth, the escape courses to remedial intercessions gave by mitochondria should likewise be viewed as future investigations into combination treatments that evacuate this adaptability will be essential to propel tumor medicines.

ACKNOWLEDGEMENT: The authors are grateful to the competent authorities of Guru Ghasidas Vishwavidyalaya, Bilaspur, and C. G. for providing necessary facilities for checking plagiarism through Urkund software.

CONFLICTS OF INTEREST: Authors declare that there are no conflicts of interest regarding this article.

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How to cite this article:
Pal DK, Pal S and Mukherjee S: Ongoing advancement in the comprehension of mitochondrial pro-gression with an exceptional spotlight on its relationship with cancer and possible therapeutic strategy. Int J Pharm Sci & Res 2021; 12(3): 1421-32. doi: 10.13040/IJPSR.0975-8232.12(3).1421-32.