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Cellular Models Derived from Patients for Polytarget Precision Medicine in Neurodegeneration Associated with Pantothenate Kinase

1.Dr.M. SREENIVASULU*, PRINCIPAL, NARAYANA PHARMACY COLLEGE
2. Sk. Salma Sultana, Asst. Professor, DEPT OF Pharmacology
3. M.V. Sai Charan, Asst. Professor, DEPT OF Pharmacy Practice
4. A. Ravi Kumar, Asso. Professor, DEPT OF Pharmacology
5. Dr.S. sujatha, Professor dept of Pharmaceutics,
[1,2,3,4,5] NARAYANA PHARMACY COLLEGE, CHINTHA REDDYB PALEM, NELLORE

Abstract: A wide range of progressive and incapacitating neurological hereditary illnesses in which iron is selectively accumulated in certain brain regions are together referred to as neurodegeneration with brain iron accumulation (NBIA).Pantothenate kinase-associated neurodegeneration (PKAN), the most common subtype of NBIA diseases, is brought on by pathologic variations in the PANK2 gene, which codes for the enzyme pantothenate kinase 2 (PANK2). There are currently no proven ways to halt the growth of these illnesses.The usefulness of patient-derived cell models as a useful instrument for identifying natural or pharmacological substances for the use of polytarget precision medicine in PKAN is covered in this study.According to a number of recent research, fibroblasts produced from PKAN patients exhibit the primary pathogenic characteristics of the illness, such as intracellular iron excess. Interestingly, all pathologic changes in PKAN fibroblasts with residual expression of the PANK2 enzyme were improved when mutant cell cultures were treated with different supplements as pantothenate, pantethine, vitamin E, omega 3, α-lipoic acid, L-carnitine, or thiamine.The data from pharmacological screens in patient-derived cellular models may be used to improve treatment plans for specific PKAN patients.

Keywords: neurodegeneration with brain iron accumulation (NBIA); pantothenate kinase-associatedneurodegeneration (PKAN); pantothenate kinase 2 (PANK2); pantothenate; pantethine; vitamin E;omega 3; α-lipoic acid; L-carnitine; thiamine; fibroblasts; induced neurons; precision medicine

Introduction

A class of rare genetic neurodegenerative diseases known as NBIA is clinicallyThey may cause early death and manifest as severe dystonia, stiffness, dysarthria, loss of ambulation, parkinsonism, choreathetotic movements, retinal degeneration or optic nerve atrophy, and mental problems [1]. Iron deposits in the basal ganglia and surrounding regions, as well as widespread axonal dilatation (referred to as spheroid bodies) in the central nervous system (CNS), which reflect degenerated neurones, are the most common pathogenic findings [2]. Currently, NBIA diseases are linked to about 15 genes [3]. However, it is uncertain what the responsive genes of roughly 20% of people with clinical suspicion of NBIA are. There are currently no viable therapies to stop the course of neurodegeneration in NBIAs, despite the significant research efforts on these disorders and the suggestions of novel therapeutic methods.New treatment approaches are thus required.One of the most common NBIA subtypes, accounting for about 50% of cases, is caused by pathological variations in the pantothenate kinase 2 (PANK2) gene, which codes for an important enzyme involved in the coenzyme A (CoA) production pathway [4]. Classic and atypical PKAN are the two main clinical types of PKAN, which encompasses a continuous phenotypic continuum.Classic PKAN has a fast neurological progression and an early childhood beginning, often in the first ten years of life. Conversely, atypical PKAN is distinguished by a slower progression of the illness and a later beginning, often occurring in the second or third decade of life [5,6]. Despite this clinical categorisation, some individuals have a late onset with rapid advancement, or an early disease onset with subtle progression. Only pathogenic variations of PANK2 cause PKAN, while the PANK gene family includes the PANK1a, PANK1b, PANK2, PANK3, and PKAN4 genes. The isoenzymes PANK1, PANK2, and PANK3 are active as dimeric complexes with various cell locations.While PANK1 and PANK3 are often found in the cytosol and nucleus [8], PANK2 is the only isoform to be expressed in mitochondria in humans and monkeys [7]. The pseudo-pantothenate kinase PANK4 has phosphatase activity, catalysing the dephosphorylation of phosphopantothenate, 4′-phosphopantetheine, and its derivatives, but lacks kinase activity [9,10]. The primary regulating process in CoA biosynthesis, which uses ATP to convert pantothenate into 4′-phosphopantothenate, is catalysed by the PANK2 enzyme.Acetyl-CoA and CoA thioesters' allosteric inhibition is the primary method for regulating PANK2 activity [11].Cavestroetal has recently examined the routes for CoA production and degradation [12].

EtiopathogenesisofPKAN

CoADeficiencyinPKAN

It is thought that low PANK2 enzyme activity brought on by PANK2 mutations hinders the manufacture of CoA, resulting in a number of metabolic changes such as impaired tricarboxylic acid cycle (TCA) and cell bioenergetics, amino acid and lipid metabolism, and ketone body formation [13,14] (Figure 1a).Furthermore, CoA also plays a role in post-translational changes (acetylation, CoAlation, acylation, and 4-phosphopantetheinylation) that regulate proteins [15].However, while CoA levels in fibroblasts produced from PKAN patients are comparable to control cells, it is unclear how CoA levels relate to PKAN pathomechanisms [16,17].Moreover, there is no experimental evidence of decreased CoA levels in human tissues lacking PANK2.Additionally, no tissue in adult pank2-KOmice showed a reduction in CoA levels [18].

These results imply that the loss of PANK2 activity may be offset by the elevated expression levels of other PANK isoforms.As a result, PKAN fibroblast cell lines showed markedly elevated expression levels of PANK1 but not

PANK3 [19].The CoA compartmentalisation hypothesis in PKAN is supported by the hypothesis that mitochondrial CoA supplies the 4'-phosphopantetheine cofactor for the posttranslational modification required to activate specific andessential mitochondrial proteins [20] (Figure 1b). However, a significant decrease in CoA levels was found in mitochondrial fractions of PKAN fibroblasts [19], indicating that a critical mitochondrial pool of CoAmmay be reduced in PKAN[20], and thus CoAlevel since alls and tissues are unaffected as the result of the compensatory increase in the other PANK isoform activities. Sequential reaction-catalyzing enzymes often function as complexes and rely on the covalent binding of a4′-phosphopantetheine cofactor to certain subunits.

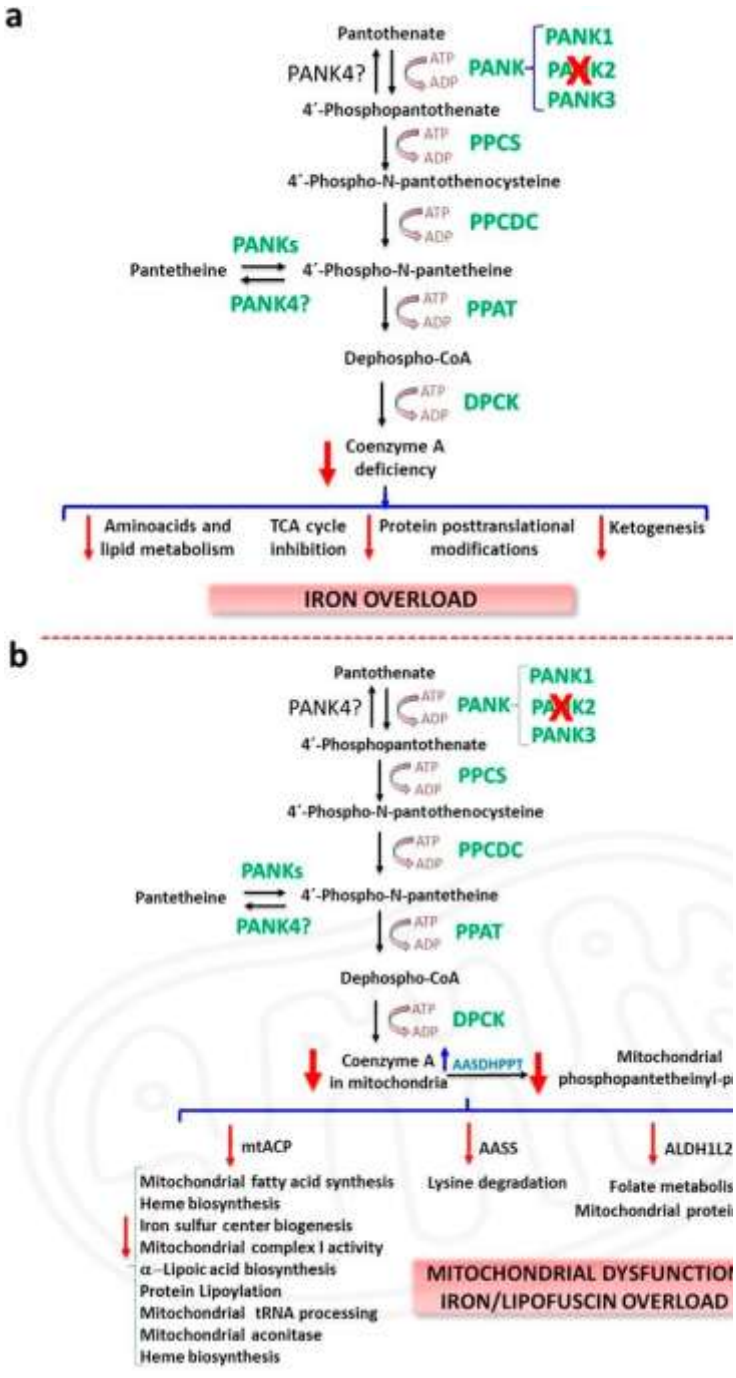


Figure 1.CoA deficiency in PKAN. (a) Etiopathogenesis of PKAN based on cellular CoA defi- ciency; (b) Etiopathogenesis of PKAN based on the deficiency of mitochondrial phosphopantetheinyl- proteins. AASDHPPT, L-aminoadipate-semialdehyde dehydrogenase-phosphopantetheinyl trans- ferase; AASS, α-aminoadipate semialdehyde synthase; ALDH1L2, Aldehyde Dehydrogenase 1 FamilyMember L2 (mitochondrial 10-formyltetrahydrofolate dehydrogenase, 10-FTHFDH); DPCK, dephos- phocoenzyme A kinase; mt ACP, mitochondrial acyl carrier protein; PKAN, pantothenatekinase– associated neurodegeneration; PPAT, phosphopantetheine adenylyl transferase; PPCDC, phosphopan-thenoylcysteine decarboxylase; PPCS, phosphopantothenoylcysteine synthetase; TCA, tricarboxylic acid cycle.

During sequential enzymatic processes, these 4′-phosphopantetheinyl proteins transport metabolic intermediates.The 4′-phosphopantetheinyl cofactor's transfer from CoA is a modification that occurs after translation [21]essential for apo-proteins to change into their fully active holoforms [21]. Therefore, 4′-phosphopantetheinylation is essential for the activity of several essential proteins, such as acyl carrier protein (ACP) involved in type I fatty acid synthesis (FAS) and mitochondrial ACP (mtACP) participating in type II mitochondrial FAS, α-aminoadipatesemialdehydes synthase (AASS) implicated in lysine metabolism, and 10-formyltetrahydrofolate dehydrogenase (10-FTHFDH), which has two isoforms: cytosolic 10-FTHFDH or ALDH1L1 (Aldehyde Dehydrogenase 1 Family Member L1) and mitochondrial 10-FTHFDH or ALDH1L2 (AldehydeDehydrogenase 1 Family Member L2) involved in folate metabolism [21] (Figure 1b). It's interesting to note that the genome of mammals only contains one distinct phosphoPTase, known as L-aminoadipate-semialdehydedehydrogenase-phosphopantetheinyltransferase (AASDHPPT) [22]. This enzyme transfers the 4′-phosphopantetheinyl cofactor to a serine amino acid in the catalytic centre of the apo-proteins after hydrolysing coenzyme A to 4′-phosphopantetheine and 3′,5′-adenosine diphosphate.Better understanding of the substrate binding and catalytic mechanism of human PPTase has been made possible by crystallisation investigations [23]. Fatty acid synthesis from acetyl-CoA and malonyl-CoA to the respective acyl carrier protein (ACP) derivatives is catalysed by the cytosolic multi-enzyme protein known as fatty acid synthase (FAS) [24]. Acyl carrier protein (ACP), malonyl/acetyltransferase, ketoacyl synthase, ketoacyl reductase, dehydrase, enoyl reductase, and thioesterase are the seven catalytic domains that make up FAS [24,25]. In order to translocate the developing fatty acyl chain intermediate from one catalytic site to another in the FAS complex, ACP, an acyl carrier, relies on its phosphopan-tetheine cofactor, which functions as a long sidearm [24,25]. The primary acyl-carrier protein involved in fatty acid biosynthesis has been identified as cytosolic ACP, which is a component of the FAS complex. Nevertheless, a distinct mtACP protein has been discovered, which differs from cytosolic ACP and bears a 4′-phosphopantetheine prosthetic group [26,27].It may be necessary for the particular mitochondrial phospho-lipid metabolism, as shown by the existence of a separate mechanism for mitochondrial fatty acid production [28, 29]. Moreover, the octanoic acid precursor needed to make the lipoic acid cofactor necessary for a number of mitochondrial proteins can only be obtained from type II mitochondrial FAS [30].The formation of a distinct fatty acid biosynthesis pathway in type II mitochondrial FAS may also be biologically significant due to the localisation of PANK2 in mitochondria and the modulation of PANK2 activity by acyl-CoA derivatives [31].

Reduced PANK2ex, in accordance with the CoAcompartmentalization hypothesis

The downregulation of mitochondrial 4′-phosphopantetheinyl proteins, including mtACP, mitochondrial10-FTHFDH (ALDH1L2), and AASS in mutant PANK2 fibroblasts [32], was linked to decreased mitochondrial CoA levels and pression levels [19].Interestingly, the enzyme that transfers 4′-phosphopantetheine from CoA has expression levels of AASDHPPT.

Certain proteins were up-regulated, most likely as a compensatory strategy to deal with low mitochondrial CoA levels and the ensuing 4′-phosphopantetheinylation deficiency. Additionally, although cytosolic 4-phosphopantetheinyl proteins like FAS and cytosolic 10-FTHFDH (ALDH1L1) exhibited normal expression levels, the low levels of phosphopantetheinyl-proteins in PKAN fibroblasts were restricted to the mitochondrial compartment [32]. Lipoylated protein levels are also anticipated to be downregulated, which is consistent with mtACP deficiency, which similarly inhibits lipoic acid production by type II mitochondrial FAS [30]. Accordingly, it has been shown that cells generated from PKAN patients had significantly reduced pyruvate dehydrogenase (PDH) lipoylation and activity [32]. Similarly, lower mitochondrial protein lipoylation and PDH activity were linked to lower MtACP levels in the CoA-deficient Drosophila model [20].Similarly, otherlipoylate denzyme activity

It is anticipated that complexes such α-ketoglutarate dehydrogenase (αKGDH) [33] may be impacted since the expression levels of lipoylated αKGDH were significantly down-regulated in Fibroblasts of PKAN [32].The lipoylation and activity of three further enzymes from the amino acid metabolism are also anticipated to be impacted by lipoic acid deficiency:branching-chain Glycine cleavage system (GCS), 2-oxoadipate dehydrogenase, and ketoacid dehydrogenase [34].Studies on these enzymes' activity in PKAN have not yet been conducted, however. Furthermore, since mtACP is involved in vital mitochondrial activities, a lack of it may potentially change a number of mitochondrial processes. In fact, mtACP, often referred to as NDUFAB1 (NADH:ubiquinoneoxidoreductase (NDU)-FAB1), is necessary for the construction of mitochondrial respiratory complex I [35, 36]. The 4′-phosphopantetheinyl alteration of mitochondrial proteins is essential for mitochondrial iron metabolism, as shown by mtACP's involvement in the iron-sulfur cluster (ISC) biosynthesis pathway and stability [37–39].According to the idea, a lack of mtACP results in decreased complex activity and ISC formation.This prediction aligns with the findings of Lambrechts et al. in Drosophila models of CoA depletion [20] and Jeong et al. in a PKAN animal model [38].Additionally, in Saccharomyces cerevisiae, the loss of mtACP results in decreased ISC production, as well as the activation of iron-responsive factors Aft1 and Aft2 and the inactivation of Fe-S cluster-dependent enzymes such aconitases, which contain a Fe-S cluster cofactor [39].Remarkably, reduced Fe-S cluster levels result in mitochondrial iron overload.[40]. Contrary to these results, aberrant iron metabolism and decreased aconitase activity have been shown in

PSC-derived neurones and fibroblasts derived from patients [41, 42].

Other researchers have similarly verified all of these hypotheses and findings using cellular models obtained from PKAN patients [32].As a result, mutant PANK2 fibroblasts showed a significant drop in mitochondrial complex I activity, cytosolic and mitochondrial complexase activities, and the expression levels of proteins involved in ISC formation [32].PKAN's Iron/Lipofuscin Accumulation

Due to its function as aversatile cofactor in several iron-containing proteins involved in cell metabolism and signalling regulation, iron is a necessary component of homeostasis [43]. Redox-active iron, on the other hand, may engage in processes that produce harmful ROS and may subsequently encourage oxidative stress, lipid/protein oxidation, nucleic acid damage [44, 45], and ultimately ferroptosis-induced cell death [46].Prussian blue staining of PKAN brain tissues revealed widespread iron accumulation in the substantia nigra, globus pallidus, and other brain regions [47]. A number of theories have been proposed to explain iron overload in PKAN.One explanation is that the process of neuronal death is the source of iron excess [48]. Therefore, in ceramide-induced apoptosis, it has been shown to enhance iron absorption [49]. However, this assumption is not supported by any more experimental evidence.Another theory links cysteine buildup brought on by insufficient PANK2 activity to deregulation of iron metabolism [50].Following pantothenic acid phosphorylation, phosphopantothenoylcysteine synthetase (PPCS) catalyses the conversion of cysteine to 4′-phosphopantothenate, which results in 4′-phosphopantothenoylcysteine.L-cysteine and its derivatives, including N-pantothenoylcysteine, may thus accumulate as a result of PANK2 activity deficiency.Because of its iron-chelating properties, elevated L-cysteine levels cause iron deposits.Furthermore, iron-induced L-cysteine oxidation may produce ROS, which would raise oxidative stress [13].Furthermore, iron-dependent lipid peroxidation, a potential secondary pathogenic process in PKAN, may be exacerbated by L-cysteine buildup, resulting in cell membrane damage and eventual cell death [13]. Thus, iron homeostasis dysregulation, elevated oxidative stress, and neurodegeneration in PKAN may be caused by the harmful consequences of cysteine buildup. The combination of dopamine, iron overload, and elevated cysteine may cause significant damage to dopaminergic neurones in PKAN illness. In the acidic environment of synaptic vesicles, dopamine is an extremely reactive chemical that does not degrade.However, unbound dopamine in the cytosol may undergo auto-oxidation processes, producing neurotoxic quinones and ROS including OH, O−2, and H2O2 [51].Numerous studies have looked at how dopamine and iron interact to produce neurotoxic intermediates [52].Briefly, iron-dependent dopamine is one of the two primary mechanisms.

The formation of o-quinones by a non-enzymatic process [53,54] and their involvement in an intermediate iron-dopamine complex [55] are neurotoxic. Furthermore, dihydrobenzothiazines (DHBTs), which are strong inhibitors of mitochondrial complex I [56] and cause a persistent rise in oxidative stress and apoptosis [57,58], may be produced when dopamine oxidation products combine with L-cysteine. Iron may accumulate in lipofuscingranules, which are significantly elevated in PKAN cells, according to an alternate explanation [19].The age pigment, lipofuscin, is a brown-yellow, electron-dense, autofluorescent aggregation that gradually builds up in senescent cells, such as neurones, hepatocytes, and cardiomyocytes [59]. Lipofuscin is a diverse combination of

metal cations, sugar residues, oxidised proteins, and lipids [59]. About 2% of the components of lipofuscin include metals, such as Fe, Cu, Zn, Al, Mn, and Ca [60]. Lipofuscingranules are not broken down in the proteasomal system, a protease complex that identifies and breaks down defective proteins [61]. According to one interpretation, mitochondria play a role in the production of lipofus-cin [62]. This theory is supported by the fact that isolated mitochondria may degenerate into lipofuscin granules in the absence of prooxidants or oxygen saturation [63]. The production of lipofuscin granules is likely to occur in degenerated mitochondria, according to electron microscope image analysis of PKAN fibroblasts (Figure 2).

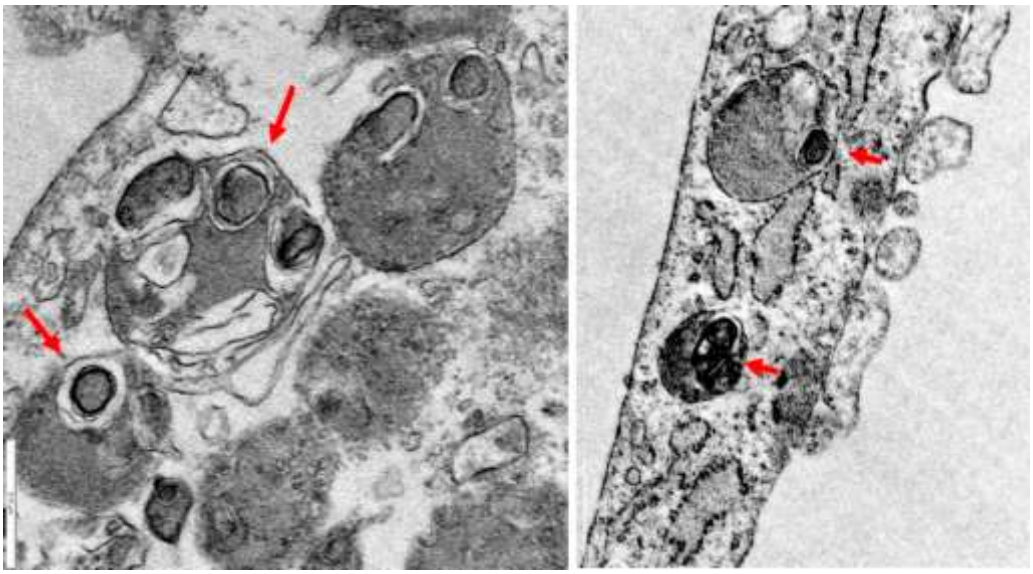


Figure2. Lipofuscin formation in mitochondria in PKAN fibroblasts. Electron microscopy images ofPKANfibroblasts(unpublisheddatafromourlaboratory). Lipofuscinformationindegenerated mitochondria, red arrows. Scale Bar = 0.5 μm.

Lipofuscinoverload is one of the most well-known indicators of ageing [64], and it has been shown that the characteristic senes-cent shape is linked to its accumulation in PKAN cells [19]. Numerous studies have shown that lipofuscin actively contributes to the physiopathological alterations of senescent cells (Figure 3) [65,66].The proteasome [67], the primary cellular protease complex responsible for breaking down damaged proteins identified by polyubiquitin chains, has been shown to be inhibited by lipofuscin. Its attachment to exposed hydrophobic caminoacid residue on the lipofuscin surface explains proteasomal inhibition [68]. By increasing sosomal permeabilization, lipofuscin may also decrease lysosomal activity [69, 70].It's interesting to note that lipofuscinogenesis is significantly aided by proteasome and lysosome suppression [61].

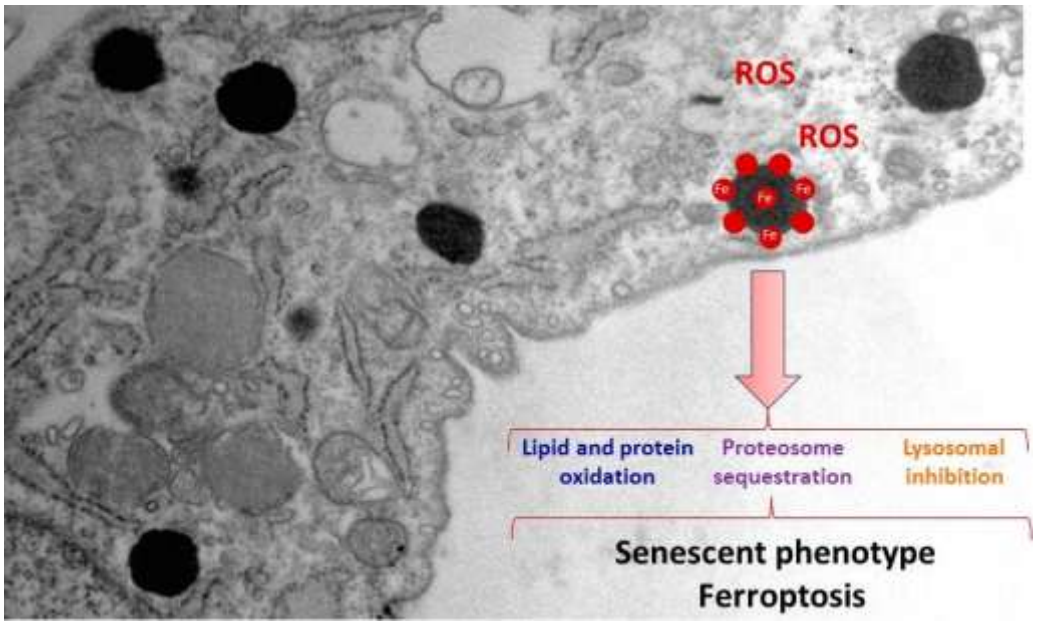


Figure3.PathologicalalterationsoflipofuscinaccumulationinPKANcells. IncreasedROSproduc- tion, cellular compounds oxidation, proteasomal sequestration and lysosomal inhibition by lipofuscin granules lead to a senescent phenotype, and eventually to cell death by ferroptosis.

The cytotoxicity of lipofuscin granules is mostly caused by the recruitment of transition metals like iron [60].Granules with a lipofuscin-trapping iron result have a dox-active surface that may catalyse the Fenton reaction (Figure 3). This characteristic of lipofuscin granules may promote the production of reactive oxygen species (ROS) and the oxidation of lipids and other cellular constituents, ultimately resulting in cell death [71]. PKAN fibroblasts have been shown to have elevated oxidative stress, which was exacerbated by the addition of iron [72]. These findings are supported by evidence of elevated carbonylated protein and mitochondrial lipid peroxidation levels in PKAN fibroblasts [19].Conjunctival fibroblasts, retinal artery pericytes, and macrophages have all been shown to have lipofuscin granules in NBIA illnesses [73]. Changes in mitochondrial ISC and heme production pathways have been linked to iron metabolism dysregulation in PKAN fibroblasts [19,41,42,72]. ISCs are prosthetic groups that are attached to cytosolic and mitochondrial aconitases, as well as several subunits of mitochondrial respiratory complexes [74].Many mitochondrial proteins may be impacted by a lack of proteins involved in ISC biogenesis, which may result in severe mitochondrial malfunction.Another consequence of this shortage is impaired iron control, which may ultimately lead to mitochondrial iron excess.High iron levels in the mitochondria's oxidative environment may then lead to a rise in ROS production, which exacerbates the damage and spreads it [75].Furthermore, the enhanced iron transport into the cells that gradually results in iron overload may be explained by inefficient mitochondrial iron utilisation linked to low cytosolic free iron (cytosolic labile iron pool, CLIP) [41]. Therefore, in a number of human cell lines, siRNA-induced PANK2 silencing results in a decreased rate of proliferation, paradoxical iron deficit, and elevated levels of transferrin receptor protein 1 (TfR1) expression [76]. In light of these findings, the theory that cytosolic iron insufficiency and mitochondrial iron excess are caused by dysregulation of iron metabolism in the mitochondria has been put forward. Increased iron intake as a consequence of elevated Fe2+transporter expression, followed by accumulation in mitochondria and, ultimately, in lipofuscin granules, is the outcome of this vicious cycle [19,77]. When thinking about the use of chelating medicines in PKAN patients, this paradoxical free iron deficit in PKAN cells may potentially be a significant consideration. Determining the aetiology of PKAN and its implications for other neurodegenerative illnesses like Parkinson's disease (PD) and Alzheimer's disease (AD) depend on our ability to comprehend the pathomechanisms of iron excess in PKAN cells. Therefore, further research in the PKAN illness model may aid in identifying certain processes that result in dysregulation of iron metabolism.

PKANDiseaseModeling

ModelingPKANDiseaseinBiologicalModels

The primary phenotypic changes associated with PKAN disease, such as brain iron overload and movement disorder symptoms, have not been accurately replicated despite numerous attempts to model the disease in various organs [38,78–87]. This could be because PANK2 localisation in the intermembrane space of mitochondria has only been shown in humans and primates. As a result, the cytosol has been shown to contain the mouse PANK2 homolog protein [7].Although a mitochondrial targeting sequence in the mouse PANK2 enzyme has not been found, other researchers have described a mitochondrial localisation [88,89]. In a PANK2 knockout mouse model, researchers observed reduced weight, retinal degeneration, and azoospermia, but no movement abnormalities or indications of iron accumulation in the brain [82]. Iron buildup in the basal ganglia was not seen, but a lack of pantothenic acid caused movement changes in the knockout mice [90]. See [91] for a thorough update of PKAN murine models.

With differing degrees of success, a number of studies have been conducted to create PKAN models in Drosophila. There is just one PANK isoform in Drosophila (fumble, fbl) [92], and its inhibition resulted in CNS problems [78], which were resolved by pantethine therapy [83]. Neurones did not, however, exhibit iron deposits.

In the zebrafish model, morpholinos' silencing of PANK2 resulted in abnormalities of the central nervous system, namely in the telencephalon, and vascular structures [87]. Another research found that zebrafish embryos with overexpressed mutant human PANK2 and mutant zebrafish PANK2mRNA had decreased locomotor activity and vascular and neurological

abnormalities [81]. Vascular problems had not been documented in any other model of PKAN, despite the fact that neurological deficits were anticipated.This discovery may point to an undiscovered function of PANK2 activity in the formation of blood vessels.

Given that the CoAbiosynthesis route is extensively conserved across humans and other organisms, modelling PKAN in S. cerevisiae may be of special relevance.Another benefit is that yeast cells are simple to manage and enable cellular and genetic tests to assess treatment approaches and investigate the effects of CoA deficiency. A unique PANK enzyme that is vital to viability is codified by the yeast PANK homolog Cab1 [80,93]. According to a recent research, the cellular abnormalities seen in cells isolated from PKAN patients are reproduced by the Cab1G315S mutation [94]. Additionally, elevated intracellular iron levels were linked to lower expression levels of important iron absorption genes, according to iron content tests [94]. To further understand the function of iron excess in PKAN, it may be interesting to investigate the processes causing this iron dysregulation in yeasts. Furthermore, mitochondrial dysfunction was shown in yeast models of PKAN, which were characterised by reduced oxygen consumption rates and activities of cytochrome c oxidase and NADH cytochrome c reductase [94]. Similarly, it has been shown that PKAN etiopathogenesis in patient-derived fibroblasts is related to mitochondrial dysfunction [20]. Because of all these factors, research on yeast may help us better understand PKAN illness.Cellular Models Derived from Patients

The lack of appropriate animal models for studying PKAN has prompted the creation of patient-derived cell models, which may be used as a complementary and alternative method for examining the disease's molecular underpinnings and assessing potential treatments. It is argued that patient-derived dermal fibroblast cultures are useful since they are readily collected from skin biopsies and may be amplified using established cell culture techniques and sent to other researchers for further research. Additionally, a variety of cell banks provide a large number of fibroblast cell lines obtained from patients. These characteristics enable the use of patient-derived fibroblast cell lines in a broad range of experiments.Studies on the cellular and biochemical properties of dermal fibroblasts produced from patients have yielded valuable insights into the pathogenic pathways behind hereditary neurodegenerative disorders [95]. This approach's reasoning is based on the assumption that, despite the fact that these illnesses mainly impact the central nervous system, cultured fibroblasts may imitate the pathological changes seen in the central nervous system and retain the unique pathogenic variation even after numerous subcultures.Patient-derived fibroblast models provide controlled investigations of strain differences and might yield crucial data for comprehending disease pathomechanisms and assessing possible treatments. Therefore, we can determine which drug and at what concentration the phenotypic changes are repaired using cell models. Furthermore, this approach takes into account the unique traits of every mutation and permits the use of personalised treatment techniques.However, considering their morphological and functional characteristics, fibroblasts are not the best model to use for examining neural dysfunction. The creation of neuronal models from individuals with hereditary neurodegenerative diseases has been facilitated by the development of new scientific methods.Induced Neurones

Since the creation of Induced Pluripotent Stem Cells (iPSCs) in 2006 [96], regenerative medicine, drug screening, and disease modelling have all benefited greatly. Disease modelling and the investigation of the underlying molecular pathways in the most afflicted cells in neurological genetic illnesses are made possible by the production of iPSC from the somatic cells of patients with these disorders and its neuronal development [97]. In this regard, it is possible to create in vitro models of NBIA illnesses, including PKAN, using iPSC production and neural differentiation. Organoids, or three-dimensional organised tissues, may be produced in addition to two-dimensional iPSC cultures. The cellular structure and architecture of human organs are replicated in this model [98].Reprogramming human iPSCs in conjunction with 3D brain organoid technology might be used as a preclinical step to shorten the time it takes for human clinical trials to follow up on animal model research. Nevertheless, there are a number of disadvantages to iPSC creation, including the time-consuming, costly, and complicated methods [99]. Additional barriers to the generation of iPSCs include genetic instability, the potential to produce tumours, and changes to mitochondrial DNA [100].

The ability to directly transdifferentiate somatic cells into another has recently been made achievable by the combination of lineage-specific transcription factors.Without going through an induced pluripotent stage, for instance, cutaneous fibroblasts may be transformed into neural cells [101]. In 2010, Wernig and colleagues combined three proneural factors (Ascl1, Brn2, and Myt1l) to conduct the first direct transdifferentiation of murine embryonic and postnatal fibroblasts into induced neurones (iNs) [102]. The basic helix-loop-helix transcription factor was later added. Foetal and postnatal human fibroblasts were converted into iNs by NeuroD1 [103]. Following these groundbreaking studies, new instruments and methods have been created with the intention of increasing neural conversion efficiency.For example, human fibroblasts were transformed into functioning neurones when microRNAs (miRNAs) like miR-9/9* or miR-124 were added to the proneural gene combination [104]. Subsequent research revealed that the combination of small molecules, proneural growth factors, and the silencing of reprogramming-inhibiting barriers like the RE-1 silencing transcription factor (REST) complex greatly increased conversion efficiency, one of the primary challenges of direct reprogramming [105–107]. Regarding the production of neurones originating from iPSCs (indirect reprogramming), direct reprogramming offers a number of advantages, including the low time requirements and the the protocols' relative simplicity [101].Additionally, unlike iPSCs, iNs preserve the donor's ageing [108] and epigenetic markers [109,110], which makes them appealing models for studying the neuronal pathophysiology of age-related illnesses. Furthermore, unlike human iPSCs, iNs derived from in vivo direct reprogramming have been shown to not develop tumours [111], which suggests that they may be appropriate for cellular regeneration therapy [112].Therefore, iNs generated by direct reprogramming may be employed in cell replacement treatment by transplantation after direct conversion in vitro or in vivo reprogramming. One intriguing strategy for treating neurodegenerative diseases is the transformation of local non-neuronal cells into neuronal phenotypes. Endogenous mouse astrocytes have therefore been shown to be directly transformed into neurones in situ [112].Direct conversion of dopaminergic neurones from striatal astrocytes has been carried out in vivo in a PD animal model

[113].Despite being in its early phases, this therapeutic method is the most promising way to convert neural reprogramming into clinical therapies [114]. Numerous neurodegenerative diseases, including NBI disorders [19,32,42,115–117], Parkinson's disease (PD) [118], Huntington disease (HD) [119], myoclonic epilepsy with ragged red fibres (MERRF) syndrome [120], as well as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome [121], have been studied through the direct reprogramming of human adult fibroblasts into iNs. Nevertheless, there are a number of drawbacks to iNs produced by direct transdifferentiation. For example, it is challenging to sustain iNs in culture since cell death is seen as early as 30 DPI (days post-infection). Given that action potentials have only been found at 80–100 DPI, this constraint could interfere with the electrophysiological characterisation of iNs [105].Additionally, throughout the transdifferentiation process, cultivated iNs group together, making it challenging to isolate individual cells for certain tests.
To sum up, the production of iNs by indirector-directed reprogramming from patient-derived fibroblasts is a highly helpful tool for both comprehending the pathophysiology of these ailments and discovering novel treatment options.Interestingly, further information on the intricate pathological relationships between neurotransmitters, iron, and other metabolic intermediates will be revealed by reprogramming fibroblasts into dopamine or GABAergic neurones.Modifications to PKAN Cellular Models
Prior reports have shown dysregulation of iron metabolism and elevated oxidative stress in fibroblasts generated from individuals with PKAN [72]. Additionally, iNs that developed from PKAN-derived iPSC showed decreased mitochondrial membrane potential and abnormal cristae morphology [41]. Remarkably, neurones generated from patients also have altered electrotrophics and mitochondrial bioenergetic deficiencies.logical patterns, as well as increased oxidative stress, mitochondrial iron-dependent pathways, and disruption of cytosolic iron homeostasis. Moreover, iron overload was also seen in neurones and iPSC-derived astrocytes from PKAN patients, simulating the human clinical phenotype [42,115,116].
Recent reports of patient-derived fibroblasts with multiple PANK2 mutations exhibiting many of the disease's pathological characteristics, including intracellular iron/lipofuscin accumulation, elevated oxidative stress, and mitochondrial dysfunction, lend credence to these findings and the applicability of cell models [19,32,122,123].
TherapeuticStrategiesforPKAN
There is currently no effective treatment for PKAN. Therefore, managing patient symptoms is the goal of current therapy [1]. While there are ongoing clinical studies including a number of substances, the primary goal of PKAN therapy is to manage the primary symptoms of the condition, such as spasticity, seizures, dystonia, or mental abnormalities [124]. However, there are now a number of promising therapy options underway [12,91].Four categories may be used to summarise these treatments:iron chelation to get rid of iron buildup in the brain; (2) supplementing with metabolites to address metabolic deficiencies in the CoA pathway; (3) activating PANK isoforms to restore the production of CoA; and (4) introducing the wild-type PANK2 gene as part of gene therapy.While some of these treatments are being tested, others have not proven effective. See [12,91,124,125] for a thorough update on the most recent PKAN therapy strategies.

Notably, there aren't many research examining autophagy modification in PKAN disease models, despite the fact that autophagy is crucial for maintaining neuronal homeostasis and pathological processes including neurodegeneration [126].Huang et al. have shown that PINK1 (PTEN-induced putative protein kinase 1), a crucial protein involved in the selective autophagy of mitochondria (mitophagy), interacts genetically with fumble (fbl), the human PANK2 homolog in Drosophila [127]. Furthermore, PINK1 loss-of-function abnormalities including mitochondrial malfunction were rescued by mitochondrial fumble overexpression. Remarkably, the PINK1 deficient phenotype was reversed by vitamin B5 derivatives, which also restored mitochondrial activity and CoA/acetyl-CoA levels [127].Method for Using Patient-Derived Cellular Models to Find Alternative Treatments for PKAN Supplementing with pantothenate, the substrate for the PANK2 enzyme, was a crucial discovery that supported the usefulness of cellular models in PKAN research. raise the levels of PANK2 expression in patient-derived fibroblasts that have pathologic variations. with residual levels of enzymes [19]. Additionally, the correction of pathological changes linked to PKAN, including iron/lipofuscin excess, elevated lipid peroxidation, and compromised mitochondrial bioenergetics, coincided with the pantothenate-mediated raising of PANK2 levels.Additionally, pantothenate's beneficial effects were verified in iNs produced by PKAN fibroblasts that were directly reprogrammed [19]. According to these findings, cell models might be a helpful method for identifying individuals who react to in vitro pantothenate supplementation and have PANK2 mutations.More significantly, these findings provide credence to the idea that large dosages of pantothenate may be used to treat them. Furthermore, our findings imply that tailored screening approaches in PKAN can make it easier to find additional pharmacological chaperones (PCs) that can raise and stabilise the expression levels and activity of the mutant PANK2 enzyme in certain mutations.

Destabilisation of the mutant proteins is a result of several mutations in human disorders. Surprisingly, substances that function as PC can restore the activity of unstable proteins [128–130]. However, based on their unique genotype, each patient will only be appropriate for PC treatment [131]. This view is supported by the fact that pantothenate can rescue some but not all of the pathogenic variations of PANK2 [19]. As a result, a method for choosing more positive PCs in PKAN cellular models may help find possible therapy solutions for individuals with certain mutations.Using this method, PCs can already be used to treat a number of rare diseases [132]: Diltiazem, an antihypertensive drug, for Gaucher disease [133]; Acetylcysteine, a mucolytic agent, for Pompe disease [135]; Ambroxol, another mucolytic agent, for Fabry and Gaucher disease [136]; Carbamazepine and dibenzazepine, for hyperinsulinemic hypoglycemia [137]; Pyrimethamine, an anti-parasitic medication, for GM2 gangliosidosis [138]; and Salicylate, a well-known anti-inflammatory drug, for Pendred syndrome [139]. An allosteric brain-permeable PANK activator (PZ-2891) has been discovered for PKAN illness [84].Under PZ-2891 treatment, an intriguing knockout mice model of brain CoA deficiency demonstrated weight increase, improved locomotor activity, and a longer lifespan [84]. By activating the other PANK isoforms, this treatment strategy seeks to compensate for the loss of PANK2 [84].PKAN

Precision Medicine

Precision medicine is a new approach that takes into account how clinical care may be tailored to each patient's unique genetic traits.Compared to the conventional "one drug fits all patients" approach, clinical precision medicine seems to be a more reasonable approach for the treatment of hereditary neurodegenerative diseases [140].Indeed, genetic Even patients with the same neurodegenerative illness or pathological variation may have different clinical features. Furthermore, it is very improbable that individuals would benefit from a single medication since several metabolic or signalling pathways may be secondary impacted.Because of the growing understanding of the genetic basis of the illness and its clinical categorisation, the growing number of biomarkers, and the potential for disease-modifying therapies, hereditary neurological disorders offer interesting models for precision medicine [141].

In this regard, patient-derived fibroblasts and iNs may be used in precision medicine techniques to optimise therapy approaches in PKAN. Precision medicine-based approaches are presently being used in a variety of medical specialities, including cardiology, nutrition, cancer, and uncommon disorders [142,143].The early precision medicine-based approaches to neurodegenerative illnesses have proved more applicable to Alzheimer's disease (AD).An anti-amyloid-β monoclonal antibody, therefore Patients with mutations known to cause AD are currently undergoing therapy testing with the goal of keeping individuals with comparable genetic changes from developing neurodegeneration (ClinicalTrials.govnumberNCT01760005, retrieved on 5May2023).Furthermore, APOE (apolipoprotein E) variations may be used to identify people who are more likely to develop AD [144], which makes them intriguing biomarkers for early diagnosis and the use of preventative and/or therapeutic measures.Although Parkinson's disease (PD) is currently treated as a single clinical entity, several researchers stress that PD contains many subgroups that potentially benefit from precision medicine techniques [145]. However, the clinical phenotypic variety and complicated nature of AD and PD provide serious obstacles to the effective use of personalised treatment in these conditions. Figure 4 depicts the key stages of a personalised medication strategy used for PKAN. First, fibroblast cultures are created by doing a skin biopsy. The primary changes of PKAN illness, including iron/lipofuscin accumulation, lipid peroxidation, senescent morphology, and mutant protein expression levels, are then examined in order to characterise fibroblasts. Apart from confirming the activity of PANK2, the expression levels of downstream proteins like mtACP are also assessed.Pharmacological screening is then done to find the compounds that can fix the changes that have been found. Indirect reprogramming generates induced neurones in parallel, confirming that they express the neural markers. Lastly, the induced neurones are examined for the positive chemicals found in the fibroblast screening. Using this approach, seven beneficial commercial supplements have recently been identified [122,123]: pantothenate, pantethine, vitamin E, omega 3, α-lipoic acid, L-carnitine, and thiamine. They were all able to reduce the buildup of iron and lipofuscin, raise the levels of PANK2 and mtACP proteins, and restore the altered phenotype in responder mice.tantcells. The idea behind pantothenate supplementation is that greater substrate concentrations may improve the activity of mutant enzymes. In vitro experiments have shown that high-dose pantothenate supplementation may enhance the activity of a functionally deficient PANK enzyme, even when the enzyme's affinity for pantothenate is low and its action remains functional [146]. These findings are intriguing because they suggest that individuals with pathogenic variations who have residual PANK2 expression levels and/or activity may benefit therapeutically from large doses of pantothenate supplementation.However, individuals with frameshift mutations that result in termination codons in both alleles that encode the production of an incomplete or truncated protein do not respond well to this treatment approach.For this reason, assessing the impact of pantothenate supplementation in vitro on patient-derived cells may provide important insights into how certain subgroups of pathogenic variants respond. In order to obtain the required functional effects in the human brain in vivo, it is also important to determine if pantothenate therapy can reach the right concentration. Increasing pantothenate concentrations in the blood and brain by combination therapy with pantothenate and other pantothenate derivatives, including pantethine, might be one way to overcome this challenge.

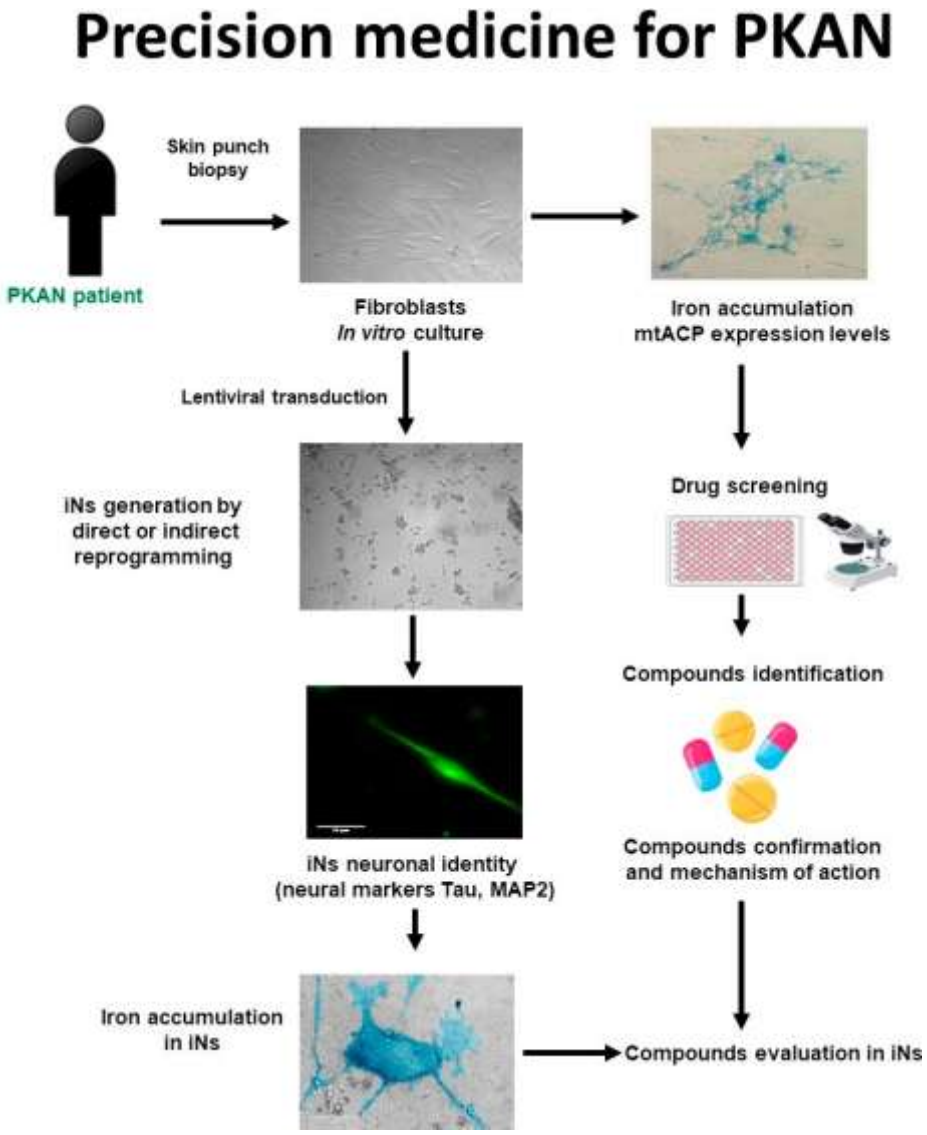


Figure 4. Cell-based disease modeling and drug screening approach in PKAN. PKAN patient-derivedcellular models, fibroblasts, and iNs, can be useful tools for mimicking pathophysiological alterationsof the disease and screening potential therapies. iNs = induced neurons; mtACP= mitochondrial acylcarrier protein.

As a metabolic intermediary in the production of CoA, panthethine is a physiological molecule that is produced from pantothenic acid and cysteine. Due to its high instability and quick conversion to pantothenate and cysteamine, pantothenate levels in the blood might rise as a result of pantothenate therapy [147,148]. It has been shown that panthethine supplementation may restore PKAN symptoms in a variety of biological models, including mice [79], zebrafish [87], Drosophila [83], and bacteria [149]. Although pantethine has been utilised as a lipid-lowering drug in human research, its therapeutic potential in PKAN has mostly been assessed in animal models [150]. Recently, fifteen children with PKAN had their safety and effectiveness with pantethine (60 mg/day for six months) assessed [151]. Pantethine supplementation did not change blood CoA levels or alleviate clinical symptoms, according to the study's findings.The limited number of patients receiving therapy, the short treatment period, and the low dosage concentration or low bioavailability of pantethine might all contribute to the study's poor therapeutic effectiveness in PKAN patients.However, taking supplements of aspantethine can raise blood concentrations of pantothenate, some people may benefit better from a combination of pantothenate and pantethine. In PKAN cellular models, oxidative stress and elevated ROS generation after iron exposure have been previously shown [72]. Alvarez-Cordoba et al. discovered elevated levels of carbonylated proteins and mitochondrial lipid peroxidation in PKAN fibroblasts, which is in line with these results [19].Lipid peroxidation is often defined as a chain process that produces lipid peroxyl radicals, hydroperoxides, and aldehyde derivatives when polyunsaturated fatty acids (PUFA) undergo oxidative damage [31]. Lipid peroxidation is said to occur in three stages: start, propagation, and termination [152]. Each of these stages' corresponding chemical reactions may be found elsewhere [153]. Lipid peroxidation disrupts the membrane's structure, changing permeability, ion transport, and fluidity [154]. Additionally, this mechanism generates a number of breakdown metabolites, including 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) [155]. Protein and DNA adducts of MDA and 4-HNE alter a number of cellular functions and take part in secondary crosslinking events that might exacerbate the disease's pathogenesis.Furthermore, lipid aldehydes may alter the activities of protein kinases and phosphatases, which might result in aberrant activity of many transcription factors that are crucial in maintaining cellular homeostasis [156]. Iron buildup in lipofuscingranules might result from lipid peroxidation in iron-rich organelles like mitochondria and changes in membrane-dependent cellular functions including vesicle trafficking and/or autophagy/mitophagy, which in turn raises lipid peroxidation of membranes [156]. The evolution of neurodegenerative illnesses like PKAN may be exacerbated and precipitated by this vicious cycle of events that reinforce one another. By halting the spread of lipid peroxidation, membrane antioxidants like vitamin E may break this vicious cycle in neurodegenerative disorders [157]. Furthermore, vitamin E is an essential component for brain function and neural growth [158].This fact, together with a wealth of data showing that oxidative stress and lipid peroxidation are linked to neurodegenerative illnesses, led to the theory that membrane antioxidants, like vitamin E, may slow the course of neurodegeneration [159].Numerous studies in human and animal models of vitamin E deprivation evaluated its role in preventing oxidative damage to the brain, particularly to the cerebellum [160]. Numerous neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), have been linked to the onset and development of lipid peroxidation [161]. Similarly, excessive ROS generation and mitochondrial redox imbalance are intimately linked to the pathomechanisms of PKAN [162]. Particularly, fibroblast and iNs generated from individuals with PKAN have been shown to exhibit lipid peroxidation and enhanced generation of ROS [41,72]. Therefore, preventing the spread of lipid peroxidation may reduce the progression and lessen the severity of PKAN illness. Numerous studies evaluating their role in various biochemical functions, such as the enhancement of antioxidant defences [163], the production of anti-inflammatory factors, the increase in fluidity of cellular membranes, and the regulation of gene expression [164–166], have established the beneficial effects of omega-3 fatty acids in the treatment of numerous disorders. It's interesting to note that supplements containing omega-3 fatty acids have been shown to have antioxidant benefits via inhibiting lipid peroxidation [167]. Furthermore, they have been connected to synaptic plasticity, which enhances cognitive function [164]. There is growing scientific evidence that omega-3 fatty acids may be effective in treating neurodegenerative illnesses in general [168,169], and AD and PD in particular [170]. A pleiotropic organosulfur molecule, α-lipoic acid is essential for both controlling gene expression and mitochondrial function and energy synthesis [171–173].α-Plants, animals, and humans all manufacture lipoic acid, which is made in mitochondria from scratch utilising iron-sulfur group intermediates, S-adenosylmethionine, and mtFASII [173].The determinant role of α-lipoic acid in oxidative metabolism is characterised by its Its neuroprotective and anti-inflammatory qualities are due to its antioxidant qualities [174].In this regard, α-lipoic acid may remove reactive nitrogen species (RNS) and ROS and lower the amounts of proinflammatory chemicals [175].Furthermore, it has been shown that supplementing with α-lipoic acid increases cellular antioxidant activity and decreases lipid peroxidation [176]. From an energetic perspective, α-lipoic acid functions as a cofactor for branched-chain ketoacid dehydrogenase, pyruvate dehydrogenase (PDH), α-ketoglutarate dehydrogenase (KDH), and protein H of the glycine cleavage system (GCS) [177–179]. Additionally, a number of research have shown that α-lipoic acid has chelating capabilities on metals like iron or copper and has a beneficial effect on lipid peroxidation and oxidative stress [180]. These results imply that α-lipoic acid is a chemical of interest for the treatment of neurodegenerative illnesses like PKAN. Supplementing with α-lipoic acid dramatically reduced iron buildup in responsive PKAN fibroblasts and iNs, supporting this theory [123]. The favourable impact of α-lipoic acid supplementation on lowering age-dependent iron overload in the rat cerebral cortex is further supported by these findings [181]. Additionally, in a zebrafish model, α-lipoic acid prevented iron overload brought on by ferric ammonium citrate supplementation [182]. In conclusion, antioxidants such vitamin E, omega 3, and α-lipoic acid may shield cell membranes from lipid peroxidation and oxidative stress, which are key clinical features of PKAN [19,32] and other NBIA illnesses [117]. L-carnitine, an aquaternary amine (3-hydroxy-4-N-trimethylaminobutyrate), which is produced from the amino acids methionine and lysine, is required for the translocation of fatty acids to the mitochondrial compartment for β-oxidation.Furthermore, by

boosting the gene expression of mitochondrial components, L-carnitine promotes mitochondrial biogenesis, aids in the metabolism of carbohydrates, and inhibits the buildup of reactive radicals or toxic compounds [183,184]. Fatty acid β-oxidation may be hampered by mitochondrial dysfunction in PKAN, which may have a selective impact on brain metabolism. Furthermore, a rise in the NADH/NAD(+) ratio caused by malfunction of the mitochondrial respiratory chain inhibits β-oxidation and, indirectly, L-carnitine deficiency [185]. L-carnitine, a naturally occurring substance that may boost cellular energy production, may thus have therapeutic promise in PKAN.Supplementing with L-carnitine has been demonstrated to improve mitochondrial activity in a number of diseases in recent studies [184,186]. Furthermore, PDH-enhancing drugs like thiamine [187] may be an intriguing adjuvant treatment since PDH deficit is a significant pathologic characteristic of PKAN.Since thiamine is a cofactor of several multimeric enzymes, including PDH and α-KGDH complexes that engage in the Krebs cycle, it has a wide range of roles in cell metabolism.Furthermore, It has been reported that thiamine therapy benefits a number of patients with
PDH deficiency brought on by mutations in the pyruvated ehydrogenase alpha subunit (E1) [188–192]. Remarkably, all positive compounds found following customised drug tests (pan- Omega3, α-lipoic acid, L-carnitine, tothenate, pantethine, vitamin E, and thiamine) in increased the amounts of PANK2 transcripts and protein expression and up-regulated important transcription factors that are involved in PANK2, including NF-Y, FOXN4, and hnRNPA/B [122,123]. expression of genes [193].Additionally, it is known that these beneficial supplements also promote mitochondrial biogenesis by expressing vital regulators including mitochondrial transcription factor A (TFAM) and peroxisome proliferator-activated receptor coactivator-1α (PGC1α) [194–196].When combined, these data provide valuable insights. The beneficial effects of pantothenate, pantothine, vitamin E, α-lipoic acid, omega 3, L-carnitine, and thiamine are attributed to molecular processes. It is hypothesised that these companies' partial correction of PANK2 expression levels Pounds may boost the mitochondrial compartment's production of CoA, which would enable 4′-phosphopantethenylation of vital mitochondrial proteins such mtACP, mitochondrial 10-FTHFDH (ALDH1L2), and AASS [20].The findings supported this theory by demonstrating that the expression levels of many 4′-phosphopantethe carrier proteins in PKAN cells were elevated in pathogenic variations that responded to therapy with pantothenate, pantethine, vitamin E, omega 3, α-lipoic acid, L-carnitine, or thiamine [122,123].
PolytargetTherapyinPKAN
Given that a number of drugs have favourable effects on PKAN cell models, it would be intriguing to investigate their therapeutic effectiveness in controlled clinical trials, either alone or in combination. In many important therapeutic areas, including cancer, Alzheimer's disease (AD), Parkinson's disease (PD), inflammation, epilepsy, depression, and other psychiatric disorders, the standard practice is to combine multiple compounds that affect different cellular pathways or processes at the same time. This approach may also be more effective in controlling complex diseases like PKAN [197–199].Therefore, creating medication combinations that control many targets might help overcome the drawbacks of monotherapies [200].
Drugs and their possible synergistic combinations may be systematically identified using cellular models taken from individuals with hereditary neurodegenerative disorders. These models can then quickly advance into preclinical research and clinical practice [201,202].
Numerous variables, including inflammation, oxidative stress, iron buildup, mitochondrial malfunction, and genetic and environmental factors, all have a role in the development of neurodegenerative disorders [203]. The multifactorial and complex character of these disorders may thus be better addressed by multitargeted treatments including antioxidant and mitochondrial-stimulating chemicals [204,205].Recently, multitarget therapy methods have emerged as a valuable tactic in the creation of possible neurological disease therapies [206]. However, given that the blood-brain barrier's transport mechanisms are necessary for substances to reach the brain and that the physicochemical properties of the molecule also influence the diffusion of these compounds, more research on the clinical effects of the beneficial compounds is necessary, taking into account their pharmacokinetics, bioavailability, and, most importantly, their ability to pass through the blood-brain barrier [207].
Conclusions
Understanding the underlying pathological mechanisms of PKAN and performing polytarget phenotypic screenings that enable the identification of compounds and their combinations capable of correcting the mutant phenotype are two benefits of using cellular models derived from PKAN patients. In addition to analysing how patient-derived cells react to various therapies, genomics, transcriptomics, proteomics, and metabolomics will provide crucial information for a more rational therapeutic approach to complicated disorders like PKAN. In this manner, the responsiveness of patient-derived cells to current therapies and the particular clinical variations might be taken into consideration when optimising treatments for PKAN illness.

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