Rzeszów University Press 2025
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2025.2.8

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2025; 23 (2): 468–481

REVIEW PAPER

The role of ABCA12 in neurodegenerative diseases – a review of molecular mechanisms and potential therapeutic implications

Daksh Kumar [1], Falguni Goel [1], Sachchida Nand Rai [2]

[1] Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology (MIET), Meerut, India
[2] Center of Experimental Medicine and Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

ABSTRACT

Introduction and aim. ABCA12 a member of the ATP-binding cassette transporter superfamily, is known to be involved in lipid transport and in the formation of the skin barrier. However, recent evidence also suggests its implication in the pathophysiology of neurodegenerative diseases. This review focuses on the molecular mechanisms that could link ABCA12 to neurodegenerative processes and its potential as a therapeutic target.

Material and methods. A literature review search was conducted between 200 and 2024 via the databases, which included PubMed, Scopus, and Web of Science. There, pertinent studies with relevance to ABCA12 involvement in neurodegenerative diseases were searched. This study reviewed pertinent articles on the expression patterns of ABCA12 and its molecular interactions, as well as its contribution to cellular processes, such as lipid homeostasis, inflammation, and neuronal integrity. The analysis further included studies on ABCA12 mutations and their associations with neurodegenerative pathologies such as Alzheimer's disease, Parkinson's disease, and Huntington's disease.

Analysis of literature. The results from the analysis showed that ABCA12 dysfunction led to disturbances in lipid metabolism, accompanied by increased oxidative stress, neuroinflammation, and compromised integrity of the neuronal membrane. The results imply that mutations or dysregulation of ABCA12 exaggerates amyloid-beta aggregation in Alzheimer's disease and dopaminergic neuron loss in Parkinson's disease. Finally, pathways of ABCA12 functionally interact with other core neurodegenerative mechanisms, which include autophagy dysregulation and mitochondrial dysfunction. Preliminary preclinical data indicate that altering ABCA12 expression or function diminishes neuroinflammation and restores cellular homeostasis.

Conclusion. ABCA12 plays an important role in maintaining neuronal health and its dysfunction contributes to neurodegenerative processes. Targeting pathways related to ABCA12 seems promising to mitigate disease progression in neurodegenerative diseases. More research is still required to elucidate its precise molecular mechanisms and identify specific interventions.

Keywords. ABCA12, central nervous system cholesterol homeostasis, lipid metabolism, neurodegenerative diseases

The list of abbreviations:

ABCA12 – ATP binding cassette transporter A12, **CNS** – central nervous system, **AD** – Alzheimer's disease, **PD** – Parkinson's disease, **HD** – Huntington's disease, **CRISPR** – clustered regularly interspaced short palindromic repeats, **NFTs** – neurofibrillary tangles, **Aβ** – amyloid beta, **αSyn** – alpha synuclein

Corresponding author: Falguni Goel, e-mail: falguni.goel@miet.ac.in or falgunigoel2908@gmail.com

Received: 10.11.2024 / Revised: 30.12.2024 / Accepted: 1.01.2025 / Published: 30.06.2025

Kumar D, Goel F, Rai SN. The role of ABCA12 in neurodegenerative diseases – a review of molecular mechanisms and potential therapeutic implications. *Eur J Clin Exp Med.* 2025;23(2):468–481. doi: 10.15584/ejcem.2025.2.8.

Introduction

ABCA12 has been considered a critical member of the family of transporters of the ATP-binding cassette (ABC), for which members have primarily been known for lipid translocation across cellular membranes, especially in skin keratinocytes.[1] Its role has been quite well characterized with respect to the function of the skin barrier, in which the major role of ABCA12 is the transport of glucosylceramides, prime constituents of the lipid bilayer as lamellar granules in the process of keratinization. Main defects in this process, attributed to mutations in the ABCA12 gene, are the major cause for a severe skin disorder known as Harlequin ichthyosis, wherein there is defective lipid transport leading to defective barrier function. This is characterized by thickened skin, severe desquamation, and a compromised epidermal barrier that often leads to life-threatening dehydration and infections. Although such a gene has been very important in maintaining health of the skin, it appears current evidence indicates that ABCA12 functions outside of skin homeostasis and lipid metabolism is central to most other tissues, particularly the, central nervous system (CNS).[2] Recent studies have shown the expression of ABCA12 in the CNS suggesting involvement in lipid metabolism within the brain.[3] Lipid homeostasis is crucial to neuronal integrity, synaptic function, and membrane fluidity, and its disruption is increasingly implicated in neurodegenerative disease pathology.[4] For example, aberrant lipid metabolism has been linked to protein aggregation, oxidative stress, and mitochondrial dysfunction in diseases like Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD).[5] ABCA12 has been known for ages to be associated with lipid trafficking. As such, dysfunction in it is thought to lead to increased imbalance in lipids that may cause neurodegeneration.[3]

Dysregulation of lipids can be neurotoxic and could influence the properties of neuron membranes, impairing membrane fluidity and composition and thus affecting synaptic plasticity and neurotransmission.[6] Moreover, lipids such as sphingolipids and ceramides play a significant role in cell signaling pathways, inflammation, and programmed cell death. Any form of dysregulation in such lipid species may worsen neurodegenerative processes.[7] For instance, AD-amyloid-β plaques and tau protein tangles, which are similar in this case, are hallmarks of the disease; both of these are modulated by lipid environments.[8] PD includes α-synuclein aggregation, which is sensitive to lipid interactions. HD also includes disturbances in lipid metabolism especially cholesterol and phospholipids that have been implicated in neuronal dysfunction and death.

These links of lipid dysregulation to neurodegeneration make ABCA12, in particular through its function in lipid trafficking, a highly promising candidate to pursue studies on neurodegenerative diseases. Dysfunction in ABCA12 could potentially lead to lipid imbalance in neurons, providing a new mechanism by which these diseases might develop and progress. Being particularly relevant because glucosylceramides are crucial to cell membrane structural integrity, its further potential role in the transport of glucosylceramide makes ABCA12 particularly relevant.[9] Disruptions in this transport pathway potentially affect the stability of neuronal membranes leading to a chain reaction and neurodegeneration.[10]

Besides mechanistic roles, ABCA12 is a promising potential therapeutic target for neurodegenerative diseases. Modulation of ABCA12 activity or correction of its dysfunction could restore lipid homeostasis, thus providing an avenue for attenuating the pathological processes that might drive neurodegeneration.[11] Targeted therapies directed at enhancing the function of ABCA12 or compensating for its loss might have much broader implications than aiding to alleviate the dermatological condition called Harlequin ichthyosis because they might influence all neurological disorders.[12] Further, ABCA12, in terms of being a therapeutic target, will lead to treatments that are aimed at gaining back balance in lipid level-a feature not yet implicated in neurodegenerative disease research.

ABCA12 has been studied for quite a long time due to its function regarding lipid transport in skin. However, because of its involvement with neurodegeneration, this might open very new fields of doing further research. The increasing strength of the evidence for expression within the CNS and critical function in lipid trafficking indicate that ABCA12 may play a very significant role in the causation of diseases like AD, PD, and HD.[13] Knowledge of the molecular mechanisms by which ABCA12 contributes to lipid dysregulation in the brain could open the gates to innovative therapeutic strategies for these devastating conditions.

Aim

This review focuses on the molecular mechanisms that could link ABCA12 to neurodegenerative processes and on its potential as a therapeutic target.

Material and methods

A thorough literature search was conducted via the databases, which included PubMed, Scopus, and Web of Science. There, pertinent studies with relevance to ABCA12 involvement in neurodegenerative diseases were searched. The articles highlighted were between 2000 and 2024. This study reviewed pertinent articles on the expression patterns of ABCA12 and its molecular interactions, as well as its contribution to cellular processes, such as lipid homeostasis, inflammation, and neuronal integrity. The analysis further included studies on ABCA12 mutations and their associations with neu-

rodegenerative pathologies such as Alzheimer's disease, Parkinson's disease, and Huntington's disease.

Analysis of the literature

Molecular structure and protein function

The ABCA12 gene is one of the largest transmembrane proteins encoded at chromosome 2q34 and belongs to the ABC transporter family.[14] Like the entire family of the ABCs, ABCA12 is composed of two nucleotide-binding domains (NBDs) and two transmembrane domains. These NBDs use the energy from the hydrolysis of ATP to transport lipids out of the plasma membrane. This opens up the possibility that ABCA12 drives glucosylceramides and other lipids into the lamellar bodies of skin cells, a necessary aspect of forming the epidermal barrier.[15]

Transport of lipids and cholesterol metabolism role of ABCA12

The central role of ABCA12 in lipid metabolism is in the transport of ceramides and glucosylceramides, both key components of the lipid bilayer that play a prominent role in maintaining membrane integrity within the neurons in the CNS while modulating synaptic transmission.[16] Another possible function of ABCA12 is in cholesterol homeostasis, since cholesterol is itself integral to the lipid bilayer and lipid rafts – the microdomains implicated in protein trafficking and signal transduction.

Potential roles in neuronal lipid regulation

Although the exact function of ABCA12 in the CNS is yet to be fully elucidated, it is clear that lipid transporters, such as ABCA12 can impact neuronal health. ABCA12 may regulate the balance of cholesterol and ceramides within the cell membranes of neurons, a balance critical for synaptic function, myelination, and neuronal survival.[3] CNS ABCA12 dysregulation could lead to lipid imbalances contributing to neurodegeneration.[17]

Factors regulating ABCA12 expression

The expression of ABCA12, a critical lipid transporter implicated in epidermal barrier function, is finely controlled by a variety of factors, including transcription factors, microRNAs, epigenetic mechanisms, lipid levels, oxidative stress, inflammation, hormonal regulation, pharmacological agents, and keratinocyte differentiation signals.[18] Understanding these regulatory mechanisms can provide insight into the molecular basis of skin homeostasis and disorders associated with ABCA12 dysfunction.[19]

Transcription factors

Specific transcription factors influence ABCA12 expression by binding to its promoter or enhancer regions. For instance, peroxisome proliferator-activated receptors (PPARs), which regulate genes involved in lipid metabolism, might directly or indirectly affect ABCA12. PPARγ, highly expressed in keratinocytes, could enhance ABCA12 expression to facilitate lipid transport necessary for forming the skin barrier. Dysregulation of such transcription factors can lead to abnormal ABCA12 levels and associated skin conditions.[1] Several transcription factors regulate ABCA12 expression:

<u>PPARs</u>

PPARs, especially PPAR-α and PPAR-γ, are nuclear receptors. They regulate lipid metabolism and skin barrier integrity, positively regulating ABCA12 transcription. This enhances lipid transport necessary for epidermal differentiation.[20] PPAR-γ and PPAR-β/δ activation was found to highly induce ABCA12 mRNA in cultured human keratinocytes in a dose- and time-dependent manner. The upregulation of ABCA12 mRNA is followed by an increase in the protein levels, thus implying a biologically significant effect. In contrast, ABCA12 expression is not significantly changed when PPAR-α or retinoic acid receptor, retinoid X receptor, or vitamin D receptors are activated.[21]

<u>Sterol regulatory element-binding protein 1</u>

Sterol regulatory element-binding protein 1 (SREBP-1) is a primary regulator of lipid biosynthesis. Direct evidence is scarce, but it can be noted that SREBP-1 is linked to the regulation of ABCA12 through its influence on expression. Related ABC transporters, such as ABCA1, have been studied extensively, providing information on mechanisms of regulation. For example, the close relative of SREBP-1 is SREBP-2.[22] This has been demonstrated to activate ABCA1 by enhancing the synthesis of oxysterol ligands that activate liver X receptors for the promotion of transcription of ABCA1. With structural and functional similarities existing between ABCA1 and ABCA12, SREBP-1 may have an indirect influence on ABCA12 through similar lipid metabolism pathways involving LXR activation.[23]

<u>Specificity protein 1 and 3 (SP1 and SP3)</u>

SP1 and SP3 directly bind to the GC-rich promoter regions of the ABCA12 gene. They respond to stress signals, differentiation, and metabolites, thereby modulating ABCA12 expression tightly. SP1 has activator function, while SP3 can act as activator or repressor under certain cellular conditions, creating a dynamic control. Thus, it can control the gene transcription at several cellular signals.

MicroRNAs

MicroRNAs, abbreviated as miRNAs, are short, non-coding RNA that modulate gene expression

post-transcriptionally.[24] Certain specific miRNAs that are targeted to the ABCA12 mRNA reduce its level of protein, thus inhibiting lipid transport and altering skin barrier formation. Important miRNAs involved in regulating ABCA12 are as follows:

miR-21

MicroRNA-21 (miR-21) is a well-characterized miRNA involved in various biological processes, including development, cancer, cardiovascular diseases, and inflammation.[25] It regulates gene expression by binding to target mRNAs, leading to their degradation or translational inhibition. As an inflammation and cell proliferation-related miRNA, it may downregulate ABCA12 expression, associating it with the dysfunctional lipid barrier in inflammatory disease.

miR-29b

MicroRNA-29b (miR-29b) is part of the miR-29 family, which includes miR-29b. This family is known to regulate various genes involved in processes such as fibrosis, apoptosis, and lipid metabolism.[26] Notably, miR-29b has been shown to target DNA methylation-related enzymes, influencing epigenetic modifications. This miRNA is related to the differentiation of skin and can target pathways associated with ABCA12, thus modulating its expression during keratinocyte maturation.[27]

Epigenetic mechanisms

Epigenetic regulation by DNA methylation and histone modifications can also significantly affect ABCA12 expression.[28] DNA methylation involves the addition of methyl groups to cytosine bases in the promoter region of CpG islands. Generally, DNA methylation suppresses gene expression, while hypermethylation of its promoter could silence transcription. For this reason, in certain disorders affecting the skin, one could anticipate this to be due to silencing of its transcription.[29] For example:

DNA methylation

DNA methylation is an epigenetic modification that involves the addition of methyl groups to cytosine residues in the DNA. The role of DNA methylation is important in the regulation of gene expression.[30] Hypermethylation of promoter regions results in gene silencing, but hypomethylation might lead to gene activation. Hypermethylation of the ABCA12 promoter region would result in gene silencing, thereby contributing to the defects of the epidermal barrier.[1]

Histone modifications

Histone modifications, including methylation and acetylation, play a significant role in the regulation of gene expression through changes in chromatin structure and accessibility.[31] These epigenetic changes can either promote or inhibit the transcription of specific genes. In the case of ABCA12, a gene involved in lipid transport in keratinocytes and critical for skin barrier function, direct studies linking histone modifications to its expression are scarce. Histone acetylation and methylation patterns influence chromatin accessibility and transcription of ABCA12, especially in the presence of environmental stressors.

Lipid levels

ABAC12 is a critical lipid transporter in keratinocytes responsible for maintaining the skin lipid barrier. Although the amount of studies directly related to systemic lipid levels with expression is limited, the knowledge on the general relationship of lipid metabolism with ABCA12 function does provide insightful knowledge.[32] ABCA12 activity is coupled with lipid metabolism Particular lipids, such as:

Ceramides

Ceramides are critical lipid components in the epidermis; they are involved in an important function of regulating ABCA12, a membrane transporter critical for lipid export in keratinocytes. The scientific evidence suggests that ceramides up-regulate the expression of ABCA12 through the signaling pathway of PPARδ. These are needed for the formation of the lipid barrier, ceramide levels can act as response to regulate ABCA12 expression.[33]

Sphingolipids

The family of diverse lipids comprises ceramides, sphingomyelins, and sphingosine-1-phosphate, all very important in regulating ABCA12 expression as a necessary transporter for lipid transport across keratinocytes.[34] However, studies suggest that certain ceramides activate this transporter through the PPARδ-mediated signaling pathway. These lipids are crucial for skin homeostasis and may regulate ABCA12 activity through signaling pathways that affect keratinocyte differentiation.[1]

Oxidative stress

Oxidative stress regulates ABCA12 expression through reactive oxygen species (ROS) mediated signaling pathways. ROS can alter the activity of transcription factors or induce epigenetic changes, resulting in dysregulated ABCA12 expression and impaired skin barrier function.[35]

Inflammation

Chronic inflammation in the skin, as in psoriasis or eczema, can affect the expression of ABCA12. The pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β, may interfere with normal lipid transport either by directly repressing the transcription

of ABCA12 or by changing the differentiation process of keratinocytes.[36] The interference leads to impaired function of the skin barrier and worsens the skin condition. Inflammatory cytokines can regulate ABCA12 expression:

TNF-α
TNF-α is a proinflammatory cytokine that significantly regulates lipid transporters, which include the ABC transporter family.[37] The expression of ABCA1 by TNF-α is mediated by the NF-κB pathway. The upregulation leads to increased cholesterol efflux during the phagocytosis of apoptotic cells, linking inflammatory signals to lipid efflux pathways. Prolonged exposure to TNF-α decreases ABCA12 expression, which affects lipid transport.[38]

IL-1β and IL-6
The cytokines change the expression pattern of ABCA12 through mechanisms dependent on altering keratinocyte proliferation and differentiation, thereby promoting inflammation and disrupting the skin barrier.[39]

Hormonal regulation
This vitamin A metabolite increases ABCA12 transcription by binding to nuclear retinoic acid receptors, which activate keratinocyte differentiation and lipid metabolism.[1] Retinoic acid generally activates genes responsible for keratinocyte differentiation and lipid transport; therefore, it is likely to promote ABCA12 expression. Corticosteroids, although anti-inflammatory, tend to suppress the expression of some skin barrier genes, which may affect ABCA12 levels.

Keratinocyte differentiation signals
The differentiation of keratinocytes, a critical process for the formation of the epidermal barrier, is tightly coupled with ABCA12 regulation. Differentiation signals, including calcium gradients and activation of epidermal growth factor receptor pathways, enhance ABCA12 expression to support lipid transport and skin barrier maturation.[27]

ABCA12 and neurodegenerative diseases
ABCA12 plays a crucial role in neurodegenerative diseases like AD, PD and HD (Fig. 1).

Lipid homeostasis in neurodegeneration
There is a crucial requirement for lipid homeostasis in neuronal function, and it has been observed that alterations in lipid metabolism can directly contribute to neurodegenerative diseases.[40] Cholesterol and ceramides are used by the CNS to maintain cell membrane integrity, synaptic function, and intracellular signaling. ABCA12 plays a critical role in lipid transport; mutations or dysfunction in ABCA12 may cause imbalances in lipids, which in turn contribute to neurodegenerative disease processes, such as protein aggregation, oxidative stress, and mitochondrial dysfunction.[41] ABCA12 in AD is characterized by the accumulation of amyloid plaques and neurofibrillary tangles (NFTs), and increasing evidence has come to indicate that lipid metabolism is a key component in these pathological processes.[3]

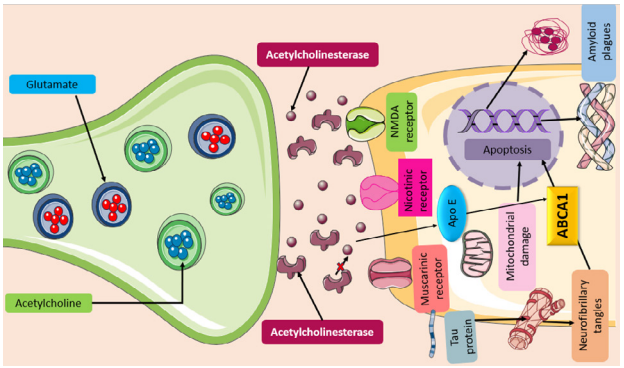

Fig. 1. Molecular pathway linking ABCA12 dysfunction via amyloid plaque formation in AD, α-synuclein aggregation in PD, and huntingtin protein aggregation in HD

Cholesterol transport and amyloid plaque formation
An essential role of cholesterol plays in Aβ plaques is the formation of the Alzheimer's disease. Dysregulation of lipid transport will probably disturb cholesterol homeostasis, and these disturbances might augment the Aβ plaque formation.[42] This interaction between cholesterol and amyloid-β peptide production takes place through the processing of APP by beta-secretase.[43] The impaired cholesterol transport could enhance amyloidogenic APP processing, thereby promoting plaque deposition.[3]

ABCA12 and tau pathology
In addition to amyloid plaques, tau protein hyperphosphorylation and aggregation into NFTs are the hallmark of Alzheimer's pathology. Lipid metabolism is considered to impact tau phosphorylation, while ABCA12, by modulating membrane lipid composition through lipid transport, indirectly acts on tau pathology. It has been suggested that levels of ceramides regulated by ABCA12 could be influential in tau aggregation and neurodegenerative processes.[44]

ABCA12 in PD
PD is typified by the aggregation of α-synuclein (αSyn) in Lewy bodies and the degeneration of dopaminergic neurons in the substantia nigra.[45] Emerging evidence ties lipid metabolism to αSyn aggregation and the development of PD.

Lipid dysregulation and αsynuclein aggregation
αSyn synuclein is a lipid-binding protein whose interaction with neuronal membranes may be enhanced by

lipid imbalance.[46] The role of ABCA12 in lipid homeostasis may play an important role in countering the misfolding and aggregation of αSyn.[47] ABCA12 disruption can impair lipid transport and alter membrane composition, thus hastening αSyn aggregation that may cause neuronal toxicity and PD.[48]

Mitochondrial dysfunction and ABCA12
Mitochondrial dysfunction is characterized by PD, and recent evidence has implicated lipid transporters such as ABCA12 in maintaining mitochondrial integrity.[49] As lipids make up a significant part of the molecules present in mitochondria, lipid transport is of significant importance for the preservation of mitochondrial membrane structure and function.[50] Lipid metabolism disruptions associated with ABCA12 may therefore lead to compromised mitochondrial function and enhanced oxidative stress and neuronal death, potentially making them contributory factors in PD pathogenesis.[51]

ABCA12 in HD
HD is one of the classic genetic neurodegenerative diseases, characterized by aggregation of the mutant huntingtin protein and progressive neuronal loss.[52]

Lipid metabolism and protein aggregation
A more recent emphasis has been placed on lipid metabolism itself, in that it could substantially contribute to the aggregation of the mutant huntingtin protein-a central aspect of HD pathology. The lipid imbalance due to ABCA12 dysfunction may accelerate huntingtin aggregation. Of the sphingolipids, ceramides are highly associated with cellular stress responses and may modify aggregation of misfolded proteins in HD.[53]

Neuronal lipid imbalance and cell death mechanisms
Synaptic function is primarily supported by membrane lipids, the homeostasis of which is essential for the survival of neurons in HD. ABCA12-mediated lipid transport can modulate the neural membrane composition.[54] Disrupted function of this protein may trigger apoptosis via the lipid-dependent pathways of cell death. Further, disrupted ceramide and cholesterol transport could facilitate increased neuronal susceptibility to stress and more rapid neurodegeneration in HD.[55]

Molecular mechanisms implicating ABCA12 in neurodegenerative processes
ABCA12, lipid rafts, and membrane dynamics in neurons
Lipid rafts are highly enriched plasma membrane microdomains mainly composed of cholesterol and sphingolipids; these microdomains play an important role in neuronal signal transduction and protein trafficking.[56]

ABCA12 regulates these lipids; aberrant ABCA12 function may disrupt the lipid raft composition and impair synaptic signaling, which seems to contribute to neurodegenerative processes.[2] Changes in lipid raft integrity have been associated with the pathology of AD and PD, where disrupted cascades of signaling promote protein aggregation and neuronal loss.[57]

Oxidative stress and neuroinflammation
Oxidative stress and chronic neuroinflammation are major characteristics of neurodegenerative diseases, and ABCA12 could influence such processes through its function in lipid transport.[58] Ceramides, whose levels the ABCA12 modulates, have been demonstrated to be implicated in neurons as oxidative and inflammatory mediators.[41] High accumulation of ceramides attributed to defective ABCA12 functionality may enhance neuroinflammatory responses and promote damage and degeneration of neurons.[2]

Lipid transport disruption and mitochondrial dysfunction
ABCA12 is essential in the maintenance of lipid balance in cellular membranes, including mitochondrial. Maintenance of high ATP production and the avoidance of ROS formation in mitochondrial membranes are contingent upon correct lipid composition.[59] Dysregulation of ABCA12 can cause mitochondrial lipid imbalance leading to mitochondrial dysfunction and oxidative stress-apoptosis in neurons, which form some of the fundamental features of diseases such as Alzheimer's and Parkinson's.[17]

Neuronal apoptosis and ABCA12 dysregulation
Neuronal apoptosis in neurodegenerative diseases often appears to be associated with disorders in lipid metabolism. ABCA12 plays a role in the protection of the cell from lipid-induced apoptosis through regulation of ceramide. Ceramides are pro-apoptotic lipids, and abnormalities in its levels due to dysfunction of ABCA12 can activate the apoptotic pathway leading to subsequent neuronal death.[60] Being able to comprehend how this dysfunction may associate with apoptotic signaling pathways in neurons might thus open fresh avenues for the investigation of neurodegenerative mechanisms.[61]

Mechanisms of endoplasmic reticulum stress and protein misfolding in ABCA12-induced neurodegeneration
ABCA12-induced neurodegeneration could be related to complicated mechanisms involving endoplasmic reticulum (ER) stress and protein misfolding. The ER has great importance in the synthesis, folding, and lipid metabolism of proteins.[62] Pathological consequences may occur in neural tissues when the ABCA12 is dysfunctional and disrupts these processes. Genetic mutations in ABCA12 can result in improperly folded proteins that fail to achieve functional conformation, accumulating in the ER. Misfolded ABCA12 may aggregate, over-

whelming the ER's protein quality control systems and leading to proteostasis imbalance.[38] Accumulated misfolded proteins activate the unfolded protein response (UPR), a protective mechanism aimed at restoring ER homeostasis. Without being resolved, chronic UPR signalling becomes inappropriate and leads to neuronal apoptosis while intensifying neurodegenerative processes.

UPR major pathways

Protein kinase RNA-like ER kinase (PERK)

The PERK pathway represents one of the major limbs of the UPR, active during ER stress.[63] PERK has a protective function to reduce the load of unfolded or misfolded proteins in the ER, however, its prolonged or otherwise dysregulated activation can lead to pathological outcomes, which are particularly pronounced in neurons.[64] When ER stress is present, PERK phosphorylates eIF2α, leading to an inhibition of global protein translation. This event avoids the accumulation of misfolded proteins in the ER and allows the cell to channel its resources towards quality control of proteins. Meanwhile, PERK-induced phosphorylation of eIF2α selectively increases the translation of ATF4, which is a transcription factor that activates genes involved in redox balance, autophagy, and amino acid metabolism.[65] But chronic activation of PERK leads to a disruption of cellular homeostasis. The availability of crucial proteins for neuronal survival and maintenance is reduced by persistent translation inhibition. In addition, extended ATF4 expression leads to the activation of CHOP (C/EBP Homologous Protein) and drives apoptotic pathways. Overactivation of PERK has been associated with synaptic dysfunction, impaired memory, and neurodegenerative diseases such as Alzheimer's and Parkinson's.[66] PERK activity also leads to interference with axonal transport and mitochondrial function that worsens neuronal vulnerability. Targeting the PERK pathway therapeutically is complex. While PERK inhibitors can mitigate neurodegeneration, they risk increasing ER stress by allowing uncontrolled protein synthesis. Balancing PERK activity remains a critical challenge in developing treatments for ER stress-related neurological diseases.[67]

Inositol-requiring enzyme 1

Inositol-requiring enzyme 1 (IRE1) is another critical sensor of ER stress and the most conserved UPR pathway. It has dual functionality: an endoribonuclease activity that processes mRNA and a kinase activity that regulates downstream signalling.[68] Upon ER stress, IRE1 autophosphorylates, thus activating its endoribonuclease domain. It splices the X-box binding protein 1 mRNA into a spliced variant known as XBP1s, a potent transcription factor that induces the genes associated with ER-associated degradation (ERAD), folding, and lipid metabolism for the efficient removal of proteins and restoration of ER homeostasis.[69] However, sustained IRE1 activity may be shifted from adaptive to maladaptive responses. Uncontrolled endoribonuclease activity causes degradation of specific mRNAs and microRNAs, disturbing cellular homeostasis. Prolonged activation also leads to inflammation due to the production of pro-inflammatory cytokines and c-Jun N-terminal kinase activation.[70] In neurons, IRE1 activity for extended periods contributes to oxidative stress and apoptosis, causing neurodegeneration. Moreover, excessive IRE1 activity enhances inflammatory cascades and, hence, it may also be related to chronic neuroinflammation, a feature of diseases such as amyotrophic lateral sclerosis and multiple sclerosis.[71]

Activating transcription factor 6

Activating transcription factor 6 (ATF6) is a transcription factor that is activated upon ER stress to improve the cell's adaptive capacity. Normally, ATF6 is a precursor residing in the membrane of the ER as an inactive form.[72] Upon the onset of ER stress, ATF6 translocates to the Golgi apparatus, where it is cleaved by site-1 and site-2 proteases. This cleavage releases its cytosolic domain, which enters the nucleus and activates genes related to protein folding, ERAD, and chaperone production.[73] ATF6 promotes the transcription of molecular chaperones like BiP/GRP78 and GRP94 to assist in the folding of proteins and in the mitigation of ER stress. The other effectors upregulate components of ERAD to ensure removal of terminally misfolded proteins. In neurons, this is crucial to maintain proteostasis and prevent the accumulation of aberrant proteins. These mechanisms, however, are compromised through the dysregulation of ATF6.[74] Reduced activity of ATF6 impairs cellular responses to ER stress and promotes protein aggregation and neurodegeneration. On the other hand, prolonged ATF6 activation leads to an imbalanced proteostasis that exhausts cellular resources and exacerbates neuronal dysfunction. In AD, where misfolded proteins overwhelm the ER, inadequate ATF6-mediated responses correlate with synaptic loss and cognitive decline.[75]

Lipid dysregulation and membrane instability

The ER is the key site for lipid synthesis and homeostasis. Dysfunctions in ABCA12 interrupt lipid transport, which can result in altered lipid composition and instability of ER membranes. Lipid dysregulation contributes to ER stress through impairment of membrane fluidity and the function of membrane-bound proteins. ABCA12 plays an important role in transporting ceramides and glucosylceramides into the cell, critical to the maintenance of membrane integrity. Deficiency of

ABCA12 impairs lipid delivery to the ER and thus affects membrane composition. The lipid imbalance disrupts ER membranes, causing stress, which makes the membranes more vulnerable to it, thus impairing the ER's ability to support protein folding and trafficking.[76] Changes in lipid composition amplify ER stress by changing the environment required for protein folding. Lipid imbalances can affect the function of resident ER chaperones and enzymes, which leads to protein misfolding and aggregation. This forms a vicious cycle, as lipid dysregulation aggravates ER stress, which in turn increases the burden of misfolded proteins.[77]

Neuroinflammatory amplification

ER stress in neurons provokes neuroinflammation, which increases the loss of neurons and enhances pathology. This reaction involves cytokine release and the activation of microglia, which are immune cells present in the brain.[78] In cytokine release ER stress-induced neuronal damage results in the release of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. These cytokines attract immune cells to the site of injury, thus increasing inflammation. Acute inflammation is protective; however, chronic cytokine release interferes with neuronal homeostasis, enhancing synaptic dysfunction and cell death. Sustained inflammation results in the activation of microglia, which then produces more pro-inflammatory mediators and ROS.[79] Overactivated microglia are part of secondary neuronal damage that creates a feedback loop in the continuation of inflammation and neuronal injury. This is the mechanism in neurodegenerative diseases such as Alzheimer's and Parkinson's, where chronic neuroinflammation accelerates the progression of the disease.[80] Targeting neuroinflammatory amplification includes inhibition of cytokine signaling or microglial modulation. Anti-inflammatory drugs and microglial inhibitors are being researched as potential therapeutic agents in neurodegenerative disorders.

Apoptotic pathways

Prolonged ER stress activates apoptotic pathways to eliminate highly damaged cells. CHOP is a transcription factor induced by sustained UPR signaling, mainly through the PERK-eIF2α-ATF4 pathway. CHOP promotes apoptosis by disrupting mitochondrial function and upregulating pro-apoptotic genes such as Bim and Bax. It also suppresses anti-apoptotic factors, thus shifting the balance toward cell death. In neurons, activation of CHOP is particularly damaging because neuronal loss leads to irreversible functional deficits.[66] CHOP's role in neurodegeneration has been well documented in ALS and Huntington's disease. Chronic ER stress activates CHOP in these conditions, leading to neuronal apoptosis and contributing to disease progression.

ABCA12-ceramide pathogenesis in neurodegeneration

Impairment in ABCA12 function leads to the accumulation of ceramide inside cells. Increased ceramide levels activate pro-inflammatory pathways, such as the NF-κB pathway, causing chronic neuroinflammation, characteristic of neurodegenerative diseases like Alzheimer's and Parkinson's.[2] Ceramide accumulation can induce oxidative stress by activating several pro-apoptotic signaling pathways. This oxidative damage is particularly harmful in neurons, which are highly vulnerable to oxidative injury.[81] Excess ceramide can also activate caspase-dependent apoptosis pathways, contributing to the loss of neurons in neurodegenerative conditions. In AD, the levels of ceramide in the brain have been reported to be high, especially in the hippocampus.[7] The imbalance in ceramide synthesis and its clearance has been related to the formation of amyloid plaques and tau tangles, which are typical features of the disease. The involvement of ABCA12 in ceramide transport may imply that disruption of this protein function will exacerbate these processes leading to neuronal loss. In PD, ceramide accumulation has been linked to dopaminergic neuron death.[41] ABCA12 dysfunction could contribute to the degeneration of these neurons, as the impaired transport of ceramide disrupts cellular functions, including synaptic vesicle trafficking and neurotransmitter release. HD has been associated with altered lipid metabolism, such as increased ceramide levels.[53] Considering the role of ABCA12 in maintaining lipid balance, its dysfunction may promote the progression of HD through enhancing neuroinflammation and cell death.

Ceramides at higher levels can disrupt the normal functioning of the cytoskeleton, which is critical for maintaining the structure and function of neurons.[82] It leads to neuronal atrophy and dysfunction. Accumulation of ceramides impairs autophagy, which is the mechanism by which cells eliminate damaged organelles and proteins.[83] In neurons, dysfunctional autophagy leads to the accumulation of toxic aggregates, such as tau and α-synuclein, associated with various neurodegenerative diseases. ABCA12 dysfunction may also affect the lipid rafts, which are membrane microdomains that play a role in cell signaling. Disruption of these lipid rafts due to the impaired ceramide transport may interfere with synaptic signaling and contribute to neuronal dysfunction.[84] Understanding the ABCA12-ceramide pathway opens avenues for potential therapeutic strategies targeting ceramide metabolism or ABCA12 activity. Modulation of ceramide metabolism or enhancement of ceramide clearance by drugs might alleviate neurotoxic effects due to its accumulation.[85] Small molecules or gene therapy approaches for enhancement of the function of ABCA12 could restore lipid transport, thus reducing pathologi-

cal effects associated with ceramide accumulation. Inhibition of inflammation pathways activated due to the accumulation of ceramide also offers a potential therapeutic avenue for neurodegenerative diseases caused by dysfunction of ABCA12.[86]

Therapeutic opportunities in the targeting of ABCA12 in neurodegenerative diseases

Manipulation of lipid transport pathways in neurodegenerative disease

However, since the ABCA12 gene participates in lipid metabolism, manipulation of lipid transport pathways might represent a novel therapeutic approach to the treatment of neurodegenerative diseases, either by normalizing lipid homeostasis through targeting the ABCA12, thus alleviating protein aggregation and oxidative stress, or through indirect compensation by an alternative lipid transport pathway in the case of ABCA12 dysfunction.[87,88]

Gene therapy and ABCA12

Gene therapy is a developing field that ensures cure for genetic dysfunctions such as those related to ABCA12.[2] In principle, gene therapy should deliver functional copies of the ABCA12 gene to affected neurons, which can correct lipid transport defects and cease the progression of neurodegenerative diseases.[89] Early-phase clinical trials of gene therapies targeting other lipid transport disorders form the basis for future ABCA12-targeted therapies.

Drug development: lipid modulators and neuroprotective agents

Restoration of lipid homeostasis in the CNS might have pharmacological interventions that could benefit neurological patients afflicted by neurodegenerative diseases.[90] Compounds that modify cholesterol and ceramide can rescue neuronal cells from lipid stress. Small molecules developed to enhance or correct imbalances through the functioning of ABCA12 may be useful candidates for neuroprotective agents, potentially retarding the progression of diseases such as Alzheimer's, Parkinson's, and Huntington's.

Challenges and future directions

Although targeting ABCA12 opens new avenues for therapy, several hurdles still need to be overcome. The CNS is a challenging environment with tightly regulated lipid metabolism; producing a change in activity of ABCA12 within this system without affecting critical pathways will require careful modulation.[87] Other research will be needed as well, to clarify ABCA12's role in the brain and its interface with other lipid transporters or pathways involved in neurodegeneration.[3]

Elucidating the function of ABCA12 in CNS lipid homeostasis

While the involvement of ABCA12 in CNS lipid homeostasis is yet to be fully determined, there are important points it controls in lipids in terms of neuronal composition and its implications in neurodegenerative processes.[44] Such points need to be studied further. Animal models in which the brain would lack or malfunction due to the absence of the ABCA12 gene may help better understand the functioning of this gene in neurodegeneration.[44]

Prospect of CRISPR-based gene therapy in ABCA12-associated therapies

CRISPR is also the revolutionary tool to correct genetic mutations. If the correct mutations in the ABCA12 gene are accurately edited by using CRISPR, it may prevent the further progress of neurodegenerative diseases that are due to ABCA12related disruption. So, there should be further investigations into the feasibility of this approach for treating the ABCA12 dysfunction within the CNS.[2]

Bridging the gap between dermatology and neurology: research on ABCA12

ABCA12 has had significant studies with dermatological disorders, but there remains an unexploited area of its function in the brain. Interconnection between studies involving ABCA12 in the skin and the CNS may be the light at the end of the tunnel in understanding its functions in lipid transport and disease on a larger scale. Hence, cross-interdisciplinary research will help further our knowledge of the role of ABCA12 in neurodegeneration.

Challenges

Lack of comprehensive models

The current animal and cell-based models fail to replicate the neural-specific effects of ABCA12 dysregulation. Such inadequacy makes it difficult to fully understand its role in the nervous system. Most models are focused on established roles in the skin, such as lipid transport in the epidermis, but ignore its unique functions in neurons.[91] The absence of models that specifically recapitulate ABCA12's neural functions makes it difficult to evaluate its contributions to processes like synaptic signaling, neuronal survival, or degeneration.

Lipid metabolism complexity

The lipid environment within the brain is unique because it's dominated by sphingolipids, gangliosides, and other complex lipids.[91] It becomes particularly challenging to study the interaction between ABCA12 with these lipids in the brain as they are very dynamic and region-specific. The diversity and complexity of lipid

profiles in the brain make it difficult to identify specific pathways affected by ABCA12.[60] The interaction of ceramides with other lipids involved in neural processes such as myelination and synaptic plasticity remains poorly understood.

Functional overlap with other transporters
ABCA12 is functionally similar to other members of the ABC transporter family.[60] Such transporters often share overlapping functions in lipid transport, making it challenging to distinguish ABCA12-specific functions. For instance, other transporters such as ABCA1 and ABCG1 are crucial in the metabolism of neural lipids and neurodegenerative diseases.[40] Elucidating the specific role of ABCA12 in these processes is a challenge.

Limited biomarkers
To date, there are no definitive biomarkers for diagnosing ABCA12 brain dysfunction.[60] This further reduces the ability to identify neural disorders at an early stage and monitor them for proper management.[92] Since specific biomarkers are lacking, monitoring the progression of neurodegenerative diseases is hard, and so is understanding the treatment efficacy or potential therapeutic value of targeting ABCA12.

Future outlooks
Creation of high-order models
More advanced models, such as neural-specific knockouts or overexpression systems, will be used to explore the role of ABCA12 in neurodegeneration.[93] Technologies such as organoids and brain-on-chip technologies can recreate the neural environment, giving deeper insights into ABCA12 function in the context of the nervous system. These models can be designed to replicate conditions such as Alzheimer's disease, Parkinson's disease, or other neurodegenerative disorders to explore ABCA12-linked mechanisms.[44]

Lipid pathway elucidation
Future research should focus on mapping out the specific roles of ABCA12 in sphingolipid and ganglioside metabolism within neurons.[94] Techniques such as mass spectrometry-based lipidomics may be used to identify specific lipid substrates and pathways affected by ABCA12 dysfunction. This may help establish direct links between ABCA12, lipid dysregulation, and specific neurodegenerative disorders.[95]

Therapeutic interventions
Small molecules or drugs, like retinoid-based therapies, can be developed to restore or modulate ABCA12 function in the nervous system. Improved systems of CRISPR and viral vectors might present with therapeutic options for correcting mutations of ABCA12 or up-regulating its expression in neural tissues. Drugs that diminish ceramide accumulation or oppose its harmful action might supplement strategies involving the modulation of ABCA12.

Multi-omics strategies
The combined genomics, lipidomics, and proteomics approaches will elucidate the functions of ABCA12 in promoting healthy neural environments. The patient-specific pattern of ABCA12 dysfunction that can be derived from multi-omics datasets opens up opportunities for precision medicine approaches. Secondary pathways and compensatory mechanisms, potentially targeted therapeutically, also are found through multi-omics approaches.[96]

Interdisciplinary research
There is a potential for researchers in dermatology, where the function of ABCA12 is better understood, and neurology, where it remains an area of exploration, to collaborate on shared mechanisms and therapeutic targets.[97] Insight from ABCA12-associated skin diseases (like harlequin ichthyosis) may have implications for its neural functions and vice versa, with a potential for better management of both dermatological and neurological disorders. Technologies and approaches in dermatology, like lipid imaging and targeted lipidomics, can be applied in neurology to better analyze ABCA12 in the brain.[34]

Conclusion

As the number of reports linking ABCA12 to lipid deregulation in neurodegenerative diseases is on the rise, this transporter is emerging as a potential therapeutic target for intervention. Activation of inhibition of ABCA12 might normalize the lipid balance against oxidative stress toward neurons and reduce protein aggregation. Future models of neurodegenerative diseases must contain lipid transport mechanisms with a role for ABCA12 so that the contribution of lipid dysregulation in disease progression can be understood better. Such integrative approaches could lead to much more effective. There is hope in personalized medicine for future treatment of neurodegenerative diseases. These distinct lipid transport dysfunctions, including mutations in ABCA12, can serve to create specific targeted therapies that address the molecular deficits underlying neurodegeneration. This research on ABCA12 shall not stop anytime soon since research in this line can greatly push forward improving the outcomes of patients affected with neurodegenerative disorders. This review now provides the ABCA12 in neurodegenerative diseases with a systematic discussion of its molecular mechanisms and therapeutic potential. Further, more detailed research will help widen the un-

derstanding of how functional dysfunction of ABCA12 propagates its effects during neurodegeneration and, more importantly, will help open up avenues for novel therapeutic strategies.

Declarations

Funding
This study did not get any grants from any agency.

Author contributions
Conceptualization, F.G. and S.R.; Methodology, F.G.; Validation, S.R., Formal Analysis, S.R.; Investigation, D.K.; Resources, F.G.; Data Curation, F.G.; Writing – Original Draft Preparation, D.K. and F.G..; Writing – Review & Editing, F.G.; Visualization, F.G.; Supervision, S.R.; Project Administration, D.K.

Conflicts of interest
All authors declared that there was no conflict of interest.

Data availability
Data will be made available as per the policy of Journal.

Ethics approval
Not applicable.

References

1. Yin X, Yan Y, Li J, et al. Nuclear receptors for epidermal lipid barrier: Advances in mechanisms and applications. *Exp Dermatol*. 2024;33(6):e15107. doi: 10.1111/exd.15107
2. Paseban T, Alavi MS, Etemad L, Roohbakhsh A. The role of the ATP-Binding Cassette A1 (ABCA1) in neurological disorders: a mechanistic review. *Expert Opin Ther Targets*. 2023;27(7):531-552. doi: 10.1080/14728222.2023.2235718
3. Behl T, Kaur I, Sehgal A, Kumar A, Uddin MS, Bungau S. The Interplay of ABC Transporters in Aβ Translocation and Cholesterol Metabolism: Implicating Their Roles in Alzheimer's Disease. *Mol Neurobiol*. 2021;58(4):1564-1582. doi: 10.1007/s12035-020-02211-x
4. Vendruscolo M. Lipid Homeostasis and Its Links With Protein Misfolding Diseases. *Front Mol Neurosci*. 2022;15:829291. doi: 10.3389/fnmol.2022.829291
5. Alqahtani T, Deore SL, Kide AA, et al. Mitochondrial dysfunction and oxidative stress in Alzheimer's disease, and Parkinson's disease, Huntington's disease and Amyotrophic Lateral Sclerosis -An updated review. *Mitochondrion*. 2023;71:83-92. doi: 10.1016/j.mito.2023.05.007
6. Mori A, Imai Y, Hattori N. Lipids: Key Players That Modulate α-Synuclein Toxicity and Neurodegeneration in Parkinson's Disease. *Int J Mol Sci*. 2020;21(9):3301. doi: 10.3390/ijms21093301
7. Chowdhury MR, Jin HK, Bae JS. Diverse Roles of Ceramide in the Progression and Pathogenesis of Alzheimer's Disease. *Biomedicines*. 2022;10(8):1956. doi: 10.3390/biomedicines10081956
8. Penke B, Szűcs M, Bogár F. Oligomerization and Conformational Change Turn Monomeric β-Amyloid and Tau Proteins Toxic: Their Role in Alzheimer's Pathogenesis. *Molecules*. 2020;25(7):1659. doi: 10.3390/molecules25071659.
9. Boer DEC, van Smeden J, Bouwstra JA, Aerts JMFG. Glucocerebrosidase: Functions in and Beyond the Lysosome. *J Clin Med*. 2020;9(3):736. doi: 10.3390/jcm9030736
10. Angelova PR. Sources and triggers of oxidative damage in neurodegeneration. *Free Radic Biol Med*. 2021;173:52-63. doi: 10.1016/j.freeradbiomed.2021.07.003
11. Mhaske A, Shukla S, Ahirwar K, Singh KK, Shukla R. Receptor-Assisted Nanotherapeutics for Overcoming the Blood-Brain Barrier. *Mol Neurobiol*. 2024;61(11):8702-8738. doi: 10.1007/s12035-024-04015-9
12. Hennies HC, Poumay Y. Skin Disease Models In Vitro and Inflammatory Mechanisms: Predictability for Drug Development. *Handb Exp Pharmacol*. 2021;265:187-218. doi: 10.1007/164_2020_428
13. Behl T, Kaur I, Sehgal A, Kumar A, Uddin MS, Bungau S. The Interplay of ABC Transporters in Aβ Translocation and Cholesterol Metabolism: Implicating Their Roles in Alzheimer's Disease. *Mol Neurobiol*. 2021;58(4):1564-1582. doi: 10.1007/s12035-020-02211-x.
14. Breuss MW, Mamerto A, Renner T, Waters ER. The Evolution of the Mammalian ABCA6-like Genes: Analysis of Phylogenetic, Expression, and Population Genetic Data Reveals Complex Evolutionary Histories. *Genome Biol Evol*. 2020;12(11):2093-2106. doi: 10.1093/gbe/evaa179.
15. Wertz PW. Lipid Metabolic Events Underlying the Formation of the Corneocyte Lipid Envelope. *Skin Pharmacol Physiol*. 2021;34(1):38-50. doi: 10.1159/000513261.
16. Budani M, Auray-Blais C, Lingwood C. ATP-binding cassette transporters mediate differential biosynthesis of glycosphingolipid species. *J Lipid Res*. 2021;62:100128. doi: 10.1016/j.jlr.2021.100128
17. Fu Y, He Y, Phan K, et al. Sex-specific lipid dysregulation in the *Abca7* knockout mouse brain. *Brain Commun*. 2022;4(3):fcac120. doi: 10.1093/braincomms/fcac120
18. Constantin AM, Mihu CM, Boşca AB, et al. Short histological kaleidoscope - recent findings in histology. Part III. *Rom J Morphol Embryol*. 2023;64(2):115-133. doi: 10.47162/RJME.64.2.01
19. Lee AY. Molecular Mechanism of Epidermal Barrier Dysfunction as Primary Abnormalities. *Int J Mol Sci*. 2020;21(4):1194. doi: 10.3390/ijms21041194
20. Wójtowicz S, Strosznajder AK, Jeżyna M, Strosznajder JB. The Novel Role of PPAR Alpha in the Brain: Promising Target in Therapy of Alzheimer's Disease and Other Neurodegenerative Disorders. *Neurochem Res*. 2020;45(5):972-988. doi: 10.1007/s11064-020-02993-5
21. Ishikawa S, Nikaido M, Otani T, et al. Inhibition of retinoid X receptor improved the morphology, localization of desmosomal proteins and paracellular permeability in three-dimensional cultures of mouse keratinocytes. *Mi-*

croscopy (Oxf). 2022;71(3):152-160. doi: 10.1093/jmicro/dfac007
22. Ye Z, Lu Y, Wu T. The impact of ATP-binding cassette transporters on metabolic diseases. *Nutr Metab (Lond)*. 2020;17:61. doi: 10.1186/s12986-020-00478-4
23. Pang B, Zhu Z, Xiao C, et al. Keratin 17 Is Required for Lipid Metabolism in Keratinocytes and Benefits Epidermal Permeability Barrier Homeostasis. *Front Cell Dev Biol*. 2022;9:779257. doi: 10.3389/fcell.2021.779257
24. Arman K, Dalloul Z, Bozgeyik E. Emerging role of microRNAs and long non-coding RNAs in COVID-19 with implications to therapeutics. *Gene*. 2023;861:147232. doi: 10.1016/j.gene.2023.147232
25. Qian H, Maghsoudloo M, Kaboli PJ, et al. Decoding the Promise and Challenges of miRNA-Based Cancer Therapies: An Essential Update on miR-21, miR-34, and miR-155. *Int J Med Sci*. 2024;21(14):2781-2798. doi: 10.7150/ijms.102123
26. Dalgaard LT, Sørensen AE, Hardikar AA, Joglekar MV. The microRNA-29 family: role in metabolism and metabolic disease. *Am J Physiol Cell Physiol*. 2022;323(2):C367--C377. doi: 10.1152/ajpcell.00051.2022
27. Lee AY. The Role of MicroRNAs in Epidermal Barrier. *Int J Mol Sci*. 2020;21(16):5781. doi: 10.3390/ijms21165781
28. Xie W, Sun H, Li X, Lin F, Wang Z, Wang X. Ovarian cancer: epigenetics, drug resistance, and progression. *Cancer Cell Int*. 2021;21(1):434. doi: 10.1186/s12935-021-02136-y
29. Yu Y, Lu S, Jin H, et al. RNA N6-methyladenosine methylation and skin diseases. *Autoimmunity*. 2023;56(1):2167983. doi: 10.1080/08916934.2023.2167983
30. Dhar GA, Saha S, Mitra P, Nag Chaudhuri R. DNA methylation and regulation of gene expression: Guardian of our health. *Nucleus (Calcutta)*. 2021;64(3):259-270. doi: 10.1007/s13237-021-00367-y
31. Zhang Y, Sun Z, Jia J, et al. Overview of Histone Modification. *Adv Exp Med Biol*. 2021;1283:1-16. doi: 10.1007/978-981-15-8104-5_1
32. Scott CA, Rajpopat S, Di WL. Harlequin ichthyosis: ABCA12 mutations underlie defective lipid transport, reduced protease regulation and skin-barrier dysfunction. *Cell Tissue Res*. 2013;351(2):281-288. doi: 10.1007/s00441-012-1474-9
33. Cui J, Christin JR, Reisz JA, et al. Targeting ABCA12-controlled ceramide homeostasis inhibits breast cancer stem cell function and chemoresistance. *Sci Adv*. 2023;9(48):eadh1891. doi: 10.1126/sciadv.adh1891
34. Vietri Rudan M, Watt FM. Mammalian Epidermis: A Compendium of Lipid Functionality. *Front Physiol*. 2022;12:804824. doi: 10.3389/fphys.2021.804824
35. Yang Y, Liu L, Tian Y, et al. Autophagy-driven regulation of cisplatin response in human cancers: Exploring molecular and cell death dynamics. *Cancer Lett*. 2024;587:216659. doi: 10.1016/j.canlet.2024.216659
36. Balić A, Vlašić D, Žužul K, Marinović B, Bukvić Mokos Z. Omega-3 Versus Omega-6 Polyunsaturated Fatty Acids in the Prevention and Treatment of Inflammatory Skin Diseases. *Int J Mol Sci*. 2020;21(3):741. doi: 10.3390/ijms21030741
37. Fan J, To KKW, Chen ZS, Fu L. ABC transporters affects tumor immune microenvironment to regulate cancer immunotherapy and multidrug resistance. *Drug Resist Updat*. 2023;66:100905. doi: 10.1016/j.drup.2022. 100905
38. Wang D, Yeung AWK, Atanasov AG. A Review: Molecular Mechanism of Regulation of ABCA1 Expression. *Curr Protein Pept Sci*. 2022;23(3):170-191. doi: 10.2174/1389203723666220429083753
39. Teramura T, Nomura T. Acute skin barrier disruption alters the secretion of lamellar bodies via the multilayered expression of ABCA12. *J Dermatol Sci*. 2020;100(1):50-57. doi: 10.1016/j.jdermsci.2020.08.010
40. Yang D, Wang X, Zhang L, et al. Lipid metabolism and storage in neuroglia: role in brain development and neurodegenerative diseases. *Cell Biosci*. 2022;12(1):106. doi: 10.1186/s13578-022-00828-0
41. García-Sanz P, Aerts J, Moratalla R. The Role of Cholesterol in α-Synuclein and Lewy Body Pathology in GBA1 Parkinson's Disease. *Mov Disord*. 2021;36(5):1070-1085. doi: 10.1002/mds.28396
42. García-Viñuales S, Sciacca MFM, Lanza V, et al. The interplay between lipid and Aβ amyloid homeostasis in Alzheimer's Disease: risk factors and therapeutic opportunities. *Chem Phys Lipids*. 2021;236:105072. doi: 10.1016/j.chemphyslip.2021.105072
43. Hanbouch L, Schaack B, Kasri A, et al. Specific Mutations in the Cholesterol-Binding Site of APP Alter Its Processing and Favor the Production of Shorter, Less Toxic Aβ Peptides. *Mol Neurobiol*. 2022;59(11):7056-7073. doi: 10.1007/s12035-022-03025-9
44. Pahnke J, Bascuñana P, Brackhan M, et al. Strategies to gain novel Alzheimer's disease diagnostics and therapeutics using modulators of ABCA transporters. *Free Neuropathol*. 2021;2:2-33. doi: 10.17879/freeneuropathology-2021-3528
45. Zhang JB, Wan XJ, Duan WX, et al. Circadian disruption promotes the neurotoxicity of oligomeric alpha-synuclein in mice. *NPJ Parkinsons Dis*. 2024;10(1):179. doi: 10.1038/s41531-024-00798-9
46. Kachappilly N, Srivastava J, Swain BP, Thakur P. Interaction of alpha-synuclein with lipids. *Methods Cell Biol*. 2022;169:43-66. doi: 10.1016/bs.mcb.
47. Smyth I, Hacking DF, Hilton AA, et al. A mouse model of harlequin ichthyosis delineates a key role for Abca12 in lipid homeostasis. *PLoS Genet*. 2008;4(9):e1000192. doi: 10.1371/journal.pgen.1000192
48. Tarling EJ, de Aguiar Vallim TQ, Edwards PA. Role of ABC transporters in lipid transport and human disease. *Trends Endocrinol Metab*. 2013;24(7):342-350. doi: 10.1016/j.tem.2013.01.006
49. Piehler AP, Ozcürümez M, Kaminski WE. A-Subclass ATP-Binding Cassette Proteins in Brain Lipid Homeosta-

sis and Neurodegeneration. *Front Psychiatry*. 2012;3:17. doi: 10.3389/fpsyt.2012.00017
50. Horvath SE, Daum G. Lipids of mitochondria. *Prog Lipid Res*. 2013;52(4):590-614.
51. Pereira CD, Martins F, Wiltfang J, da Cruz E Silva OAB, Rebelo S. ABC Transporters Are Key Players in Alzheimer's Disease. *J Alzheimers Dis*. 2018;61(2):463-485. doi: 10.3233/JAD-170639
52. Ciurea AV, Mohan AG, Covache-Busuioc RA, et al. Unraveling Molecular and Genetic Insights into Neurodegenerative Diseases: Advances in Understanding Alzheimer's, Parkinson's, and Huntington's Diseases and Amyotrophic Lateral Sclerosis. *Int J Mol Sci*. 2023;24(13):10809. doi: 10.3390/ijms241310809
53. Burtscher J, Pepe G, Maharjan N, et al. Sphingolipids and impaired hypoxic stress responses in Huntington disease. *Prog Lipid Res*. 2023;90:101224. doi: 10.1016/j.plipres.2023.101224
54. Xiao C, Rossignol F, Vaz FM, Ferreira CR. Inherited disorders of complex lipid metabolism: A clinical review. *J Inherit Metab Dis*. 2021;44(4):809-825. doi: 10.1002/jimd.12369
55. Torres M, Parets S, Fernández-Díaz J, et al. Lipids in Pathophysiology and Development of the Membrane Lipid Therapy: New Bioactive Lipids. *Membranes (Basel)*. 2021;11(12):919. doi: 10.3390/membranes11120919
56. Ouweneel AB, Thomas MJ, Sorci-Thomas MG. The ins and outs of lipid rafts: functions in intracellular cholesterol homeostasis, microparticles, and cell membranes: Thematic Review Series: Biology of Lipid Rafts. *J Lipid Res*. 2020;61(5):676-686. doi: 10.1194/jlr.TR119000383
57. Moll T, Marshall JNG, Soni N, Zhang S, Cooper-Knock J, Shaw PJ. Membrane lipid raft homeostasis is directly linked to neurodegeneration. *Essays Biochem*. 2021;65(7):999-1011. doi: 10.1042/EBC20210026
58. Kotlyarov S, Kotlyarova A. The Role of ABC Transporters in Lipid Metabolism and the Comorbid Course of Chronic Obstructive Pulmonary Disease and Atherosclerosis. *Int J Mol Sci*. 2021;22(13):6711. doi: 10.3390/ijms22136711
59. Nicholls DG. Mitochondrial proton leaks and uncoupling proteins. *Biochim Biophys Acta Bioenerg*. 2021;1862(7):148428. doi: 10.1016/j.bbabio.2021.148428
60. Pasello M, Giudice AM, Scotlandi K. The ABC subfamily A transporters: Multifaceted players with incipient potentialities in cancer. *Semin Cancer Biol*. 2020;60:57-71.
61. Manju, Bharadvaja N. Exploring the Potential Therapeutic Approach Using Ginsenosides for the Management of Neurodegenerative Disorders. *Mol Biotechnol*. 2024;66(7):1520-1536. doi: 10.1007/s12033-023-00783-2
62. Basseri S, Austin RC. Endoplasmic reticulum stress and lipid metabolism: mechanisms and therapeutic potential. *Biochem Res Int*. 2012;2012:841362. doi: 10.1155/2012/841362
63. Ricciardi CA, Gnudi L. The endoplasmic reticulum stress and the unfolded protein response in kidney disease: Implications for vascular growth factors. *J Cell Mol Med*. 2020;24(22):12910-12919. doi: 10.1111/jcmm.15999
64. Lanzillotta C, Zuliani I, Tramutola A, et al. Chronic PERK induction promotes Alzheimer-like neuropathology in Down syndrome: Insights for therapeutic intervention. *Prog Neurobiol*. 2021;196:101892. doi: 10.1016/j.pneurobio.2020.101892
65. Kalinin A, Zubkova E, Menshikov M. Integrated Stress Response (ISR) Pathway: Unraveling Its Role in Cellular Senescence. *Int J Mol Sci*. 2023;24(24):17423. doi: 10.3390/ijms242417423
66. Shi M, Chai Y, Zhang J, Chen X. Endoplasmic Reticulum Stress-Associated Neuronal Death and Innate Immune Response in Neurological Diseases. *Front Immunol*. 2022;12:794580. doi: 10.3389/fimmu.2021.794580
67. Lanzillotta C, Di Domenico F. Stress Responses in Down Syndrome Neurodegeneration: State of the Art and Therapeutic Molecules. *Biomolecules*. 2021;11(2):266. doi: 10.3390/biom11020266
68. Bashir S, Banday M, Qadri O, et al. The molecular mechanism and functional diversity of UPR signaling sensor IRE1. *Life Sci*. 2021;265:118740. doi: 10.1016/j.lfs.2020.118740
69. Tak J, Kim YS, Kim SG. Roles of X-box binding protein 1 in liver pathogenesis. *Clin Mol Hepatol*. doi: 10.3350/cmh.2024.0441
70. Qiu L, Zheng X, Jaishankar D, et al. Beyond UPR: cell-specific roles of ER stress sensor IRE1α in kidney ischemic injury and transplant rejection. *Kidney Int*. 2023;104(3):463-469. doi: 10.1016/j.kint.2023.06.016
71. Gebert M, Sobolewska A, Bartoszewska S, et al. Genome-wide mRNA profiling identifies X-box-binding protein 1 (XBP1) as an IRE1 and PUMA repressor. *Cell Mol Life Sci*. 2021;78(21-22):7061-7080. doi: 10.1007/s00018-021-03952-1
72. Turishcheva E, Vildanova M, Onishchenko G, Smirnova E. The Role of Endoplasmic Reticulum Stress in Differentiation of Cells of Mesenchymal Origin. *Biochemistry (Mosc)*. 2022;87(9):916-931. doi: 10.1134/S000629792209005X
73. Christianson JC, Jarosch E, Sommer T. Mechanisms of substrate processing during ER-associated protein degradation. *Nat Rev Mol Cell Biol*. 2023;24(11):777-796. doi: 10.1038/s41580-023-00633-8
74. Medinas DB, Hazari Y, Hetz C. Disruption of Endoplasmic Reticulum Proteostasis in Age-Related Nervous System Disorders. *Prog Mol Subcell Biol*. 2021;59:239-278. doi: 10.1007/978-3-030-67696-4_12
75. Koszła O, Sołek P. Misfolding and aggregation in neurodegenerative diseases: protein quality control machinery as potential therapeutic clearance pathways. *Cell Commun Signal*. 2024;22(1):421. doi: 10.1186/s12964-024-01791-8
76. Casado ME, Huerta L, Marcos-Díaz A, et al. Hormone-sensitive lipase deficiency affects the expression of SR-BI, LDLr, and ABCA1 receptors/transporters involved in cellular cholesterol uptake and efflux and disturbs fertility in

mouse testis. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2021;1866(12):159043. doi: 10.1016/j.bbalip.2021.159043
77. Uddin MS, Tewari D, Sharma G, et al. Molecular Mechanisms of ER Stress and UPR in the Pathogenesis of Alzheimer's Disease. *Mol Neurobiol*. 2020;57(7):2902-2919. doi: 10.1007/s12035-020-01929-y
78. Uddin MS, Yu WS, Lim LW. Exploring ER stress response in cellular aging and neuroinflammation in Alzheimer's disease. *Ageing Res Rev*. 2021;70:101417. doi: 10.1016/j.arr.2021.101417
79. Rodríguez-Gómez JA, Kavanagh E, Engskog-Vlachos P, et al. Microglia: Agents of the CNS Pro-Inflammatory Response. *Cells*. 2020;9(7):1717. doi: 10.3390/cells9071717
80. Rauf A, Badoni H, Abu-Izneid T, et al. Neuroinflammatory Markers: Key Indicators in the Pathology of Neurodegenerative Diseases. *Molecules*. 2022;27(10):3194. doi: 10.3390/molecules27103194
81. Jaganjac M, Milkovic L, Zarkovic N, Zarkovic K. Oxidative stress and regeneration. *Free Radic Biol Med*. 2022;181:154-165. doi: 10.1016/j.freeradbiomed.2022.02.004
82. McInnis JJ, Sood D, Guo L, et al. Unravelling neuronal and glial differences in ceramide composition, synthesis, and sensitivity to toxicity. *Commun Biol*. 2024;7(1):1597. doi: 10.1038/s42003-024-07231-0
83. Bao HN, Yin J, Wang LY, et al. Aberrant accumulation of ceramides in mitochondria triggers cell death by inducing autophagy in Arabidopsis. *J Exp Bot*. 2024;75(5):1314-1330. doi: 10.1093/jxb/erad456
84. Cerasuolo M, Di Meo I, Auriemma MC, Paolisso G, Papa M, Rizzo MR. Exploring the Dynamic Changes of Brain Lipids, Lipid Rafts, and Lipid Droplets in Aging and Alzheimer's Disease. *Biomolecules*. 2024;14(11):1362. doi: 10.3390/biom14111362
85. Pan Y, Li J, Lin P, et al. A review of the mechanisms of abnormal ceramide metabolism in type 2 diabetes mellitus, Alzheimer's disease, and their co-morbidities. *Front Pharmacol*. 2024;15:1348410. doi: 10.3389/fphar.2024.1348410
86. Dubot P, Sabourdy F, Levade T. Human genetic defects of sphingolipid synthesis. *J Inherit Metab Dis*. doi: 10.1002/jimd.12745
87. Behl T, Sehgal A, Grover M, et al. Uncurtaining the pivotal role of ABC transporters in diabetes mellitus. *Environ Sci Pollut Res Int*. 2021;28(31):41533-41551. doi: 10.1007/s11356-021-14675-y
88. Porokhovnik LN, Pisarev VM, Chumachenko AG, et al. Association of NEF2L2 Rs35652124 Polymorphism with Nrf2 Induction and Genotoxic Stress Biomarkers in Autism. *Genes (Basel)*. 2023;14(3):718. doi: 10.3390/genes14030718
89. Warnecke A, Giesemann A. Embryology, Malformations, and Rare Diseases of the Cochlea. Embryologie, Fehlbildungen und seltene Erkrankungen der Cochlea. *Laryngorhinootologie*. 2021;100(S01):S1-S43. doi: 10.1055/a-1349-3824
90. Teixeira MI, Lopes CM, Amaral MH, Costa PC. Current insights on lipid nanocarrier-assisted drug delivery in the treatment of neurodegenerative diseases. *Eur J Pharm Biopharm*. 2020;149:192-217. doi: 10.1016/j.ejpb.2020.01.005
91. Ramot Y, Böhm M, Paus R. Translational Neuroendocrinology of Human Skin: Concepts and Perspectives. *Trends Mol Med*. 2021;27(1):60-74. doi: 10.1016/j.molmed.2020.09.002
92. Filipek PA, Accardo PJ, Ashwal S, et al. Practice parameter: screening and diagnosis of autism: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society. *Neurology*. 2000;55(4):468-479. doi: 10.1212/wnl.55.4.468
93. Pal D, Rao MRS. Long Noncoding RNAs in Pluripotency of Stem Cells and Cell Fate Specification. *Adv Exp Med Biol*. 2017;1008:223-252. doi: 10.1007/978-981-10-5203-3_8
94. Soreghan B, Thomas SN, Yang AJ. Aberrant sphingomyelin/ceramide metabolic-induced neuronal endosomal/lysosomal dysfunction: potential pathological consequences in age-related neurodegeneration. *Adv Drug Deliv Rev*. 2003;55(11):1515-1524. doi: 10.1016/j.addr.2003.07.007
95. Chen X, Song Y, Song W, et al. Multi-omics reveal neuroprotection of Acer truncatum Bunge Seed extract on hypoxic-ischemia encephalopathy rats under high-altitude. *Commun Biol*. 2023;6(1):1001. doi: 10.1038/s42003-023-05341-9
96. Kanapeckaitė A, Burokienė N. Insights into therapeutic targets and biomarkers using integrated multi-'omics' approaches for dilated and ischemic cardiomyopathies. *Integr Biol (Camb)*. 2021;13(5):121-137. doi: 10.1093/intbio/zyab007
97. Hashimoto S, Takanari H, Compe E, Egly JM. Dysregulation of LXR responsive genes contribute to ichthyosis in trichothiodystrophy. *J Dermatol Sci*. 2020;97(3):201-207. doi: 10.1016/j.jdermsci.2020.01.012