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Improving mitochondria-associated endoplasmic reticulum membranes integrity as converging therapeutic strategy for rare neurodegenerative diseases and cancer

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A B S T R A C T

Membrane contact sites harbor a distinct set of proteins with varying biological functions, thereby emerging as hubs for localized signaling nanodomains underlying adequate cell function. Here, we will focus on mitochondria-associated endoplasmic reticulum membranes (MAMs), which serve as hotspots for Ca^{2+} signaling,

Abbreviations: ACC, Adrenocortical carcinoma; ATAD3A, ATPase family AAA-domain containing protein 3A; Bcl-2, B cell lymphoma 2; CISD2, CDGSH iron sulfur domain 2; CHMP2B, Charged multivesicular body protein 2B; CHCHD10, Coiled-coil-helix-coiled-coil-helix domain-containing protein 10; CLL, Chronic lymphocytic leukemia; CYP46A1, Cytochrome P450 family 46 subfamily A member 1; DP, Dopaminergic; DLBCL, Diffuse large B cell lymphoma; DIDMOAD, Diabetes insipidus, diabetes mellitus, optic nerve atrophy, and deafness; ER, Endoplasmic reticulum; ERM, Endoplasmic reticulum membrane; FIG4, Factor-induced gene 4; fPD, Familial Parkinson's disease; fALS, Familial Amyotropic lateral sclerosis; GLP-1, Glucagon-like peptide-1; GRP75, Glucose-regulated protein 75; HYS, Harel-Yoon syndrome; HD, Huntington's disease; IMM, Inner mitochondrial membrane; IP_3R, Inositol 1,4,5-triphosphate receptor; KTP, Kinetin triphosphate; LADC, Lung adenocarcinoma; MCU, Mitochondrial Ca^{2+} uniporter; mPTP, Membrane permeability transition pore; MAMs, Mitochondrial associated membrane; MFF, Mitochondrial fission factor; Mfn1/2, Mitofusin 1/2; MN, motor neuron; MOMP, mitochondrial outer membrane permeabilization; NCS1, Neuronal calcium sensor 1; ND, Neurodegenerative disorder; NOX2, NADPH oxidase 2; NSCLC, Non-small cell lung carcinoma; NFAT, Nuclear factor of activated T-cell; OMM, Outer mitochondrial membrane; PTPIP51, Protein tyrosine phosphate interacting protein 51; PKM2, Protein kinase M2; PP2A, Protein phosphatase 2A; PINK1, PTEN induced kinase 1; PML, Promyelocytic leukemia; PTEN, Phosphatase and tensin homolog; ROCK2, Rho-associated protein kinase 2; ROS, Reactive oxygen species; RyR2, Ryanodine receptor type 2; S1R, Sigma-1 receptor; SERCA, Sarco-endoplasmic reticulum calcium ATPase; TDP43, Tar-DNA binding protein; TIA1, T-cell-restricted intracellular antigen-1; TAF15, TATA-box binding protein associated factor 15; TG2, Transglutaminase type 2; TUBA4A, p62/sequestosome-1, tubulin alpha-4 A; TMX1, Theoredoxin-related transmembrane protein 1; UPR, Unfolded protein response; USP30, Ubiquitin Specific Peptidase 30; VDAC1, Voltage-dependent anion channel type 1; VCP, Valosin-containing protein; VAPB, Vesicle-associated protein B; WFS1, Wolframin; WS1/2, Wolfram syndrome 1/2; 6-OHDA, 6-hydroxydopamine.

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Wolfram syndrome
Familial Parkinson's disease
Amyotrophic lateral sclerosis
Harel-Yoon syndrome
ATAD3A related disorders
Cancer
Metabolomics
Calcium signaling
Endoplasmic reticulum stress
Mitochondria quality control

redox regulation, lipid exchange, mitochondrial quality and unfolded protein response pathway. A network of MAM-resident proteins contributes to the structural integrity and adequate function of MAMs. Beyond endoplasmic reticulum (ER)-mitochondrial tethering proteins, MAMs contain several multi-protein complexes that mediate the transfer of or are influenced by Ca^{2+}, reactive oxygen species and lipids. Particularly, IP_3 receptors, intracellular Ca^{2+}-release channels, and Sigma-1 receptors (S1Rs), ligand-operated chaperones, serve as important platforms that recruit different accessory proteins and intersect with these local signaling processes. Furthermore, many of these proteins are directly implicated in pathophysiological conditions, where their dysregulation or mutation is not only causing diseases such as cancer and neurodegeneration, but also rare genetic diseases, for example familial Parkinson's disease (PINK1, Parkin, DJ-1), familial Amyotrophic lateral sclerosis (TDP43), Wolfram syndrome1/2 (WFS1 and CISD2), Harel-Yoon syndrome (ATAD3A). In this review, we will discuss the current state-of-the-art regarding the molecular components, protein platforms and signaling networks underlying MAM integrity and function in cell function and how their dysregulation impacts MAMs, thereby driving pathogenesis and/or impacting disease burden. We will highlight how these insights can generate novel, potentially therapeutically relevant, strategies to tackle disease outcomes by improving the integrity of MAMs and the signaling processes occurring at these membrane contact sites.

1. Introduction

Mitochondria-associated endoplasmic reticulum (ER) membranes or MAMs are highly dynamic functional contact sites between the ER and mitochondria involved in ER stress regulation, calcium signaling, lipid transfer (for detailed review see [1,2]), mitochondrial dynamics and quality control, reactive oxygen species (ROS) production, inflammation, apoptosis and others [3,4]. For the purpose of this review, we will specifically focus on four of these physiological processes where MAMs play a substantial role, namely 1. Ca^{2+} signaling, 2. ER stress, 3. ER-mitochondria tethering and 4. mitochondria quality control (Fig. 1).

Calcium signaling is one of the best recognized physiological implication of MAMs. A large number of proteins is involved in ER-mitochondrial contact formation and subsequent ER-mitochondria Ca^{2+} fluxes. The main proteins required for mitochondrial Ca^{2+} influx include IP_3R, promoting the release of Ca^{2+} ions from the ER lumen and the mitochondrial voltage-dependent anion channel type 1 (VDAC1), transducing Ca^{2+} over the outer mitochondrial membrane (OMM) [5]. Glucose-regulated protein 75 (GRP75) acts as a chaperone between the two membrane channels [6]. IP_3Rs not only function as Ca^{2+}-transport systems at the MAMs but also contribute as ER-mitochondrial tethering proteins, thus promoting ER-mitochondrial contact site formation independently of IP_3R's Ca^{2+}-flux properties. Among the three isoforms, IP_3R2 isoform displays the highest efficiency in mediating ER-mitochondrial Ca^{2+} transfer [7]. Ca^{2+} then enters the mitochondrial lumen by crossing the inner mitochondrial membrane (IMM) via the mitochondrial Ca^{2+} uniporter (MCU), aided by the negative mitochondrial potential [8]. This tethering between ER and mitochondria allows for local Ca^{2+} signaling through Ca^{2+} microdomains, overcoming the low affinity for Ca^{2+} uptake by mitochondria [9]. Recent work using molecular rules physically controlling ER-mitochondrial distances revealed that ~20 nm distance between ER and mitochondria is optimal to support ER-mitochondrial Ca^{2+} transfer and mitochondrial oxidative phosphorylation [10]. Setting ER-mitochondrial distances lower or higher than 20 nm both reduces the efficiency of ER-mitochondrial Ca^{2+} exchanges. Among MAM proteins, the Sigma-1 receptor (S1R) is attracting much attention for its role as a chaperone at the edge of several signaling pathways. S1R is a highly conserved ER transmembrane protein enriched in MAMs, where it interacts with several proteins involved in ER-mitochondria Ca^{2+} transfer and/or activation of the ER stress pathways [11]. By stabilizing the conformation of IP_3R at MAMs, S1R increases Ca^{2+} efflux into mitochondria. During ER stress, S1R dissociates from BiP and binds IP_3R3, thereby stabilizing these channels at the MAMs and enhancing the efflux of Ca^{2+} from the ER into

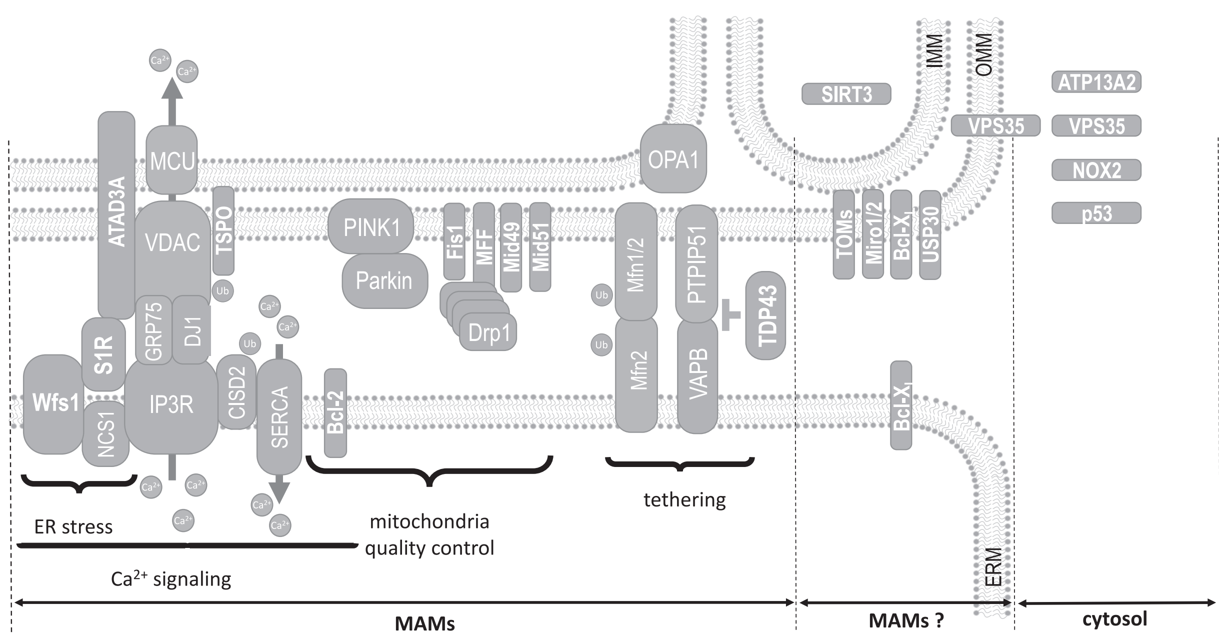

Fig. 1. Selected proteins of the mitochondria-associated membranes (MAMs). Panel 'MAMs?' depicts proteins where the MAM localization of the protein has not been fully confirmed yet. Panel 'cytosol' depicts proteins that are 1. localized in the cytosol, but have a significant impact for MAM functioning and 2. localized in cytosol, but under specific circumstances can relocate to MAMs.

the mitochondria [11–13], thus improving mitochondrial function. Indeed, a direct impact of S1R activity on mitochondrial physiology and oxidative respiration has been reported [14,15]. Wolframin gene (*WFS1*) and CDGSH iron sulfur domain 2 (*CISD2*), mutated in rare disorder Wolfram syndrome (WS) 1 and 2 encode transmembrane proteins of the ER [16]. The impact of WFS1 and CISD2 on ER-mitochondria Ca^{2+} transfer and in ER stress regulation is well documented, this includes functional interaction of WFS1 and S1R [17], WFS1 and CISD2, with Ryanodine receptor type 2 (RyR2) [18] as well as direct interaction of WFS1 and CISD2 with sarco-endoplasmic reticulum calcium ATPase (SERCA) type 2 [18,19]. Another MAMs located binding partner of WFS1 is the Neuronal calcium sensor1 (NCS1), so far known for its modulatory function to various channels including IP_3R, potassium channels and dopamine receptors. Another important component of MAMs is the protein DJ-1 linked to Parkinson's disease (PD), regulating the integrity and function of ER-mitochondria through its role in stabilizing the IP_3R-GRP75-VDAC protein complex [20]. Another amyotrophic lateral sclerosis (ALS) related MAM protein located particularly in the OMM interacting with VDAC is TSPO. Although the function of TSPO has not been fully resolved yet, its complex behaviour includes beyond the impact to VDAC mediated mitochondrial calcium entry also the regulation of mitophagy, ROS production and membrane permeability transition pore (mPTP). Probably the most complex/overwhelming involvement in the context of complex MAM functions represents the protein ATPase family AAA-domain containing protein 3A (ATAD3A) with transmembrane domains linking the outer and inner mitochondrial membrane and playing physiological role both in the mitochondrial matrix and in cytoplasm including MAMs. Indeed, although this ATAD3A related disorders protein was identified less than 10 years ago, its function covers all the focus areas of this review, i.e. calcium signaling, ER stress, mitochondrial dynamics and quality control. Beyond ATAD3A there are several additional MAM harboring proteins involved in mitochondrial dynamics and mitochondrial quality control in rare neurodegenerative diseases (NDs) and cancer. Regarding mitochondrial dynamics, which includes mitochondrial fusion, fission and mitochondrial movement, mitofusins (Mfn1/2) interactions facilitate contact formation and subsequent fusion of the mitochondrial membranes [21]. Mfn1 resides exclusively in OMM and Mfn2 has been identified both in outer mitochondrial and ER membrane. Relevance of this tethering process and subsequent mitochondrial fusion has been, in addition to ATAD3A related disorders, documented for fPD, fALS as well as in oncologic conditions. An additional ER-mitochondria tethering mechanism observed in fALS and cancer involves interaction between the vesicle-associated protein B (VAPB) in the ER and the OMM protein tyrosine phosphatase interacting protein 51 (PTPIP51) [22]. The opposite process, mitochondrial fission, is strictly affected by ER, as the ER network creates precursor rings on the mitochondrial surface. Mitochondrial fission itself requires GTPase Drp1, which promotes fission by forming oligomers and utilizing GTP-hydrolysis to constrict these oligomeric rings. However, Drp1 alone cannot bind to OMM to initiate the oligomerization, it must be recruited by OMM-located proteins such as Fis1, MFF, Mid49 and−/or Mid51. OMM located Miro1/2 are the key proteins interacting with the dynein/kinesin facilitating mitochondrial movement along the microtubules. Miro proteins possess a unique structure characterized by two Rho GTPase domains and two regulatory Ca^{2+}-binding domains, known as EF-hands [23]. Moreover, the Parkinson's disease-associated serine/threonine kinase PINK1 and ubiquitin ligase Parkin coordinate the ubiquitination of several MAM proteins including VDAC [24,25], CISD2 [26] and Mfn2 [27], as part of the mitochondrial degradation labeling process. Notably, Miro1 is one of the substrates tagged by Parkin following mitochondrial damage [28].

ER-mitochondrial contact sites have emerged as critical signaling hubs (Fig. 1), whose deregulation contributes to oncogenesis as well as several other diseases including neurodegeneration. MAMs could serve as a potential therapeutic target for rare MAM-related neurodegenerative diseases (NDs) [29] and cancer [30]. This is underscored by the fact that genes related to mitochondrial and ER homeostasis are clearly overrepresented in several rare NDs [31–33]. Due to these facts, in this review we have focused on the role of MAMs in cancer and four rare NDs, where the impact of particular MAM proteins represents key roles in their pathophysiology: Wolfram syndrome (WFS1 and CISD2), familial Parkinson's disease (PINK1, Parkin, DJ-1), Amyotrophic lateral sclerosis (S1R) and Harel-Yoon syndrome (ATAD3A).

Therefore, the aim of this review is 1. to summarize the current knowledge of MAM involvement for four specific rare NDs, namely Wolfram syndrome (WS), familial Parkinson's disease (fPD), amyotrophic lateral sclerosis (ALS), Harel-Yoon syndrome (HYS), as well as in cancer; 2. to integrate the common MAM-related pathomechanisms within these disorders, highlight the overlapping pathways and at the same time to pin the 'white spots' for the future research and 3. to present currently available therapies in term to stimulate the paradigm shift toward new therapeutic targets across diseases mentioned above to point out for putative drug repurposing in the clinical practice.

2. MAMs in Wolfram syndrome

Wolfram syndrome (OMIM #222300) is a rare neurodegenerative disorder characterized by diabetes insipidus, diabetes mellitus, optic nerve atrophy and sensorineural hearing loss – deafness [34] (therefore DIDMOAD as an alternative name), originally described by Wolfram and Wagener in 1938. Other symptoms may be present such as neurological issues (cerebellar ataxia, atrophy of the pons, epilepsy…), psychiatric symptoms (anxiety bipolar disorder, aggressiveness…) and urological problems. Currently, there is no effective treatment available, and patients typically die of central dysphagia or respiratory failure around the age of 35 [34]. Two types of Wolfram syndrome have been described in the literature, Wolfram syndrome type 1 (WS1) and Wolfram syndrome type 2 (WS2) (Fig. 2).

WS1 is caused by mutations in the *WFS1* gene, which encodes the protein wolframin. WFS1 is a transmembrane resident ER protein with nine putative transmembrane domains and is highly expressed in the brain, pancreas, heart and in lesser amounts in other organs [35]. The physiological role of WFS1 has not been fully elucidated yet, what we know so far, WFS1 plays a role in the regulation of the ER stress through the unfolded protein response (UPR) [36], regulates Ca^{2+} homeostasis [37] and impacts mitochondrial function [38]. Building on the previously mentioned points and considering the symptoms of optic nerve atrophy, deafness and overall physical weakness observed in WS1 patients, the initial clinical description led to the hypothesis that WS1 might be a mitochondrial disease [39]. However, this hypothesis was challenged by the identification of the *WFS1* gene in 1998 [40,41] and the subsequent localization of the wolframin protein to the ER membrane [42]. Therefore, in order to better understand how an ER protein deficit may be suspected to be responsible for WS symtoms typical for mitochondrial diseases (optical atrophy, deafness), the group of Benjamin Delprat looked for binding partner of the N-terminal part of WFS1 using a two hybrid screening experiment [43]. Interestingly, one identified prey was the neuronal calcium sensor 1 (NCS1), a modulator of the inositol trisphosphate receptor (IP_3R), one of the principal ER calcium channel [44]. IP_3Rs allow the proper transfer of calcium from the ER lumen toward the mitochondrial matrix [45]. Indeed, this calcium is critical for the proper functioning of three dehydrogenases of the Krebs cycle (pyruvate dehydrogenase, isocitrate dehydrogenase and α-ketoglutarate dehydrogenase) and for the complex III and V [46]. So, we hypothesized that if the activity of the IP_3R is altered, this will impair the function of the mitochondria. In this respect, NCS1 was described as a modulator of various channels as IP_3Rs, potassium channels [47], or dopamine receptors [48] with cytosolic localization. Therefore, we first determined if NCS1 would also be expressed in the MAMs using cellular fractionation. Interestingly, NCS1 was also detected in MAMs fraction, validating this hypothesis [43]. Afterward, using WS1 patients' fibroblasts, it has been demonstrated in this work that the expression level of

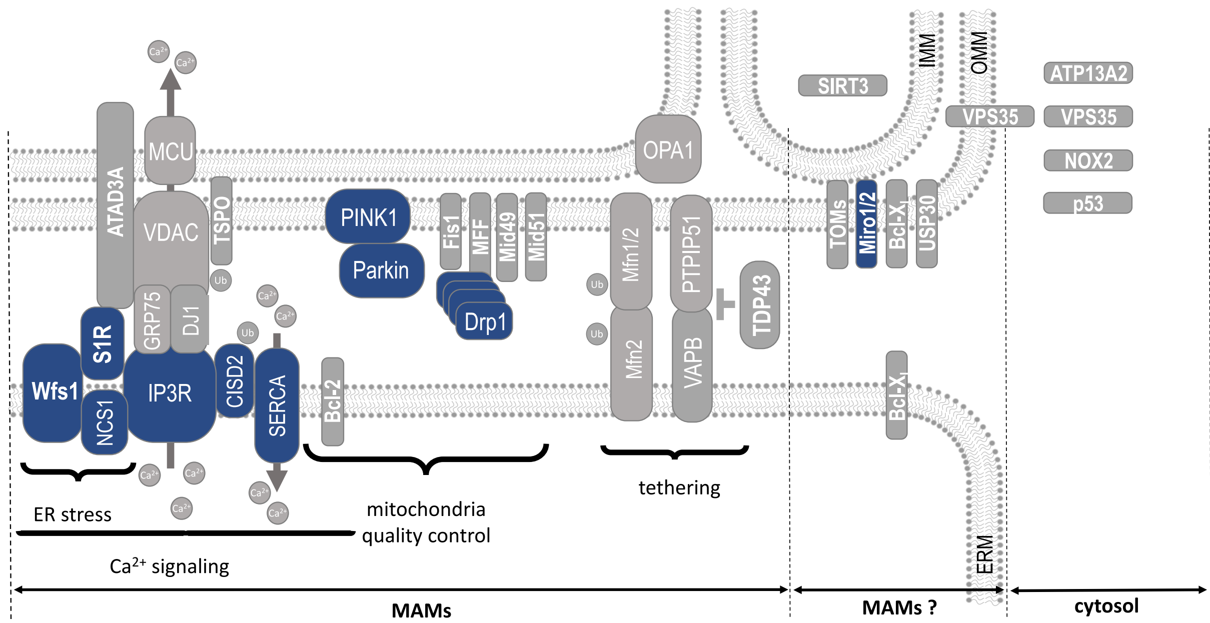

Fig. 2. Highlighted in blue: MAM proteins associated with Wolfram syndrome. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

NCS1 is reduced by half and that the number of contact and the size of the contacts between the ER and the mitochondria are reduced. Moreover, this WFS1 diminution decreased the calcium transfer from the ER to the mitochondria and the mitochondria function is altered [43]. Specifically, the complexes I and II respiratory rate and the complex I enzymatic activity are decreased. Very interestingly, WFS1 knock-down by siRNA in controls' fibroblasts led to the same NCS1 protein expression level decrease, suggesting that one of the role of WFS1 is to protect NCS1 from the degradation. In addition, knock down of NCS1 in control fibroblasts mimicked all the cellular alterations ($[Ca^{2+}]_c$, $[Ca^{2+}]_m$ are decreased, complexes I and II respiratory rate are decreased, the number of contact between ER and mitochondria are decreased) observed in WS1 patients' fibroblasts whereas NCS1 overexpression in WS1 patients' fibroblasts restored completely these deficits [43]. Altogether, these data suggest that, in fact, NCS1 is the culprit of the observed alterations via its direct regulation of the IP_3Rs.

In line with the observations described above, in rat primary cultured neurons *Wfs1* silencing causes a drop in ER Ca^{2+} stores [18] followed by diminished IP_3R-controlled ER Ca^{2+} release [18,38], depressed mitochondrial and elevated axoplasmic Ca^{2+} levels [18]. In addition, *Wfs1* silencing elevates ER stress in these neurons [38]. To support the evidence that WFS1 impacts mitochondrial tethering, recent studies have shown that wolframin silencing in primary cultured neurons leads to a reduction in ER-mitochondrial contacts and drop in mitochondrial fusion frequency resulting in mitochondrial fragmentation [18]. Although, interestingly, the mRNA expression of all main proteins involved in mitochondrial fusion, fission and movement was not changed in the brain of wolframin-deficient mice. In addition, focused on mitochondria quality control, *Wfs1* silencing induces enhanced mitophagy, documented as depressed number of autolysosomes in neurons. All these specific effects result in a significant delay in neuronal outgrowth. Importantly, most of these neuronal negative phenotypes can be rescued either by calcium transfer correction (overexpression of IP_3R fragment, overexpression of plasma membrane ORAI1, SERCA2b overexpression, treatment with L-type Ca^{2+} channel activator Bay K 8644, RyR2 silencing), by ER stress inhibition (ER chaperon HSPA5), by mitophagy inhibition (PINK1/Parkin silencing), by mitochondria fission suppression (negative dominant Drp1) or by mitochondrial dynamics stimulation (Miro1 overexpression) [18,38]. However, it is important to note that the role of wolframin in ER stress suppression appears to be complex. In these neurons, mitophagy blocking (via PINK1/Parkin silencing was not able to rescue the negative ER stress phenotype [38].

To further study the effect of WFS1 on the tissues highly expressing WFS1, beyond the zebrafish model [49] a mouse model of wolframin deficiency [50] and later a rat model of Wfs1 invalidation [51] has been developed. These two rodent models enable detailed study of Wfs1 function not only in the brain and pancreas but also in the heart. Although calcium ions are the principal trigger for myocyte contraction, Wfs1 is highly expressed in the heart tissue [35] and involved in calcium signaling, surprisingly, cardiac symptoms in WS1 cases are rarely reported. Therefore calcium transients and contractility in the Wfs1 exon5 deficient rats has been evaluated by the team of Cagalinec and Plaas in 2019 [52]. Already at the early age, i.e. excluding diabetic condition, the calcium transients and contractility of the freshly isolated left ventricular myocytes were negatively affected. Moreover, they have observed adaptive changes of myocyte membrane system and t-tubule network [52]. In line with this, the lack of functional wolframin has led to decreased expression of sarcolemmal sodium-calcium exchanger [53], demonstrating the complex effect of Wfs1 on ventricular myocyte membrane systems.

WS1 was traditionally considered as an autosomal recessive disorder, but dominant mutations in the *WFS1* gene are emerging and causing a wider range of sub-phenotypes from isolated hearing loss [54] or diabetes [55], through optic atrophy and hearing loss combination [56] to severe neonatal onset [57] in WS1 patients. All clear loss-of-function *WFS1* mutations (frameshift and nonsense) are recessive, pointing to the fact that one functional *WFS1* allele is sufficient for maintaining WFS1 function. On the other side, missense mutations will behave as recessive if they cause either loss of function or only decrease the function in various amounts. Or, they can act in a dominant negative manner - either by misfolding and causing ER stress itself, or by gaining a function that results in a decrease of ER Ca^{2+} level, thus causing ER stress again. However, also recessive mutations as p.P724L or p.G695V were found to aggregate within ER and not on the ER membrane [57]. Thus, it is possible, that part of the recessive missense mutations is causing ER stress as well but not sufficiently to induce the disease itself. To further study the *WFS1* mutations, a humanized mouse model was generated reproducing the E864K mutation [58–63], and the audition was analyzed. This mutation led to a profound deafness probably due to an impairment of the stria vascularis, the peculiar structure that generates the endocochlear potential [64]. Notably, the mutation decreases the membrane expression level of the beta subunit of the Na^+/K^+-ATPase [64]. This validated the description of the interaction of WFS1 with this subunit [65] in vitro. In addition, this mutation leads to an alteration of the MAM, associated with an alteration of autophagy and mitophagy [66].

Recently, the work of Liiv and colleagues (2024) has further explored the impact of protein CISD2, which is mutated in WS2, on MAMs function (Fig. 2). They confirmed CISD2's localization in MAMs through immunoprecipitation (IP) with wolframin, proximity ligation assay, and computational docking model. Additionally, CISD2 silencing in primary cultured neurons resulted in a drop in ER and mitochondrial calcium level, while simultaneously elevated axoplasmic Ca^{2+} levels. Next, CISD2 and RyR2 interaction as well as CISD2 interaction with SERCA2 has been confirmed by IP. Importantly, perturbations caused by CISD2 silencing can be corrected by overexpression of SERCA2b. CIDS2 associated impact to MAMs mitochondria quality control has been documented as increased mitophagy and depressed mitochondrial density in CISD2 silenced condition. Finally, diminished ER-mitochondria tethering for neuronal CISD2 silencing has been approved by MAMtracker luminescence [18]. At the MAMs, CISD2 also appears to impact Bcl-2, another protein residing at MAMs and interacting with CISD2 via its N-terminal BH4 domain [67]. A fascinating interplay between Bcl-2 and CISD2 exists at the MAMs, since overexpression of CISD2 alleviated the decreased ER-mitochondrial contact site formation evoked by Bcl-2 overexpression. Consequently, the reduction in ER-mitochondrial Ca^{2+} transfers upon Bcl-2 overexpression was counteracted by co-expression of CISD2. The role of the Bcl-2/CISD2 complex at the ER-mitochondrial interface for mitochondrial function and overall cellular health requires further study.

This progress on better understanding of wolframin role in the physiology of MAMs offers the possibility to identify novel therapeutic targets. Here, the drug dantrolene, an inhibitor of the RyR, was tested as a treatment of siRNA *Wfs1* knockout cells where it decreased intracellular Ca^{2+} level and apoptosis resulting from ER stress [68]. However, this therapeutic approach may not be optimal for dominant mutations, where chemical chaperons would be probably more appropriate therapeutics. Recently, in another cellular model of WS1, various treatments were applied to correct neuronal calcium levels and mitochondrial health. These treatments included the SERCA activator (CDN1163), an inhibitor of Ca^{2+} release via RyR (azumolene), an inhibitor of Ca^{2+} leak through the RyR (Rycal S107), a selective inhibitor of the mitochondrial Na^+/Ca^{2+} exchanger (CGP37157). In addition, intriguingly, the first-line choice treatment for WS patients liraglutide, the GLP-1 receptor agonist, reversed mitochondrial fragmentation, ATP level and mitophagy in axons with WFS1 deficit. All these drugs were very encouraging as all of these treatments were protective in regard of Ca^{2+} homeostasis and mitochondrial metabolism (with CGP37157 being effective in all parameters tested), although the positive effect of liraglutide needs further investigation to unravel its direct impact on MAMs. [18]. Another promising target may be the S1R. In general, S1R may be modulated by small molecules that can act as agonists, antagonists, or positive/negative modulators [69,70]. Therefore, we evaluated the potential positive impact of S1R's activation in preclinical models of the pathology including the WS1 patients' fibroblasts, the *Wfs1*$^{\Delta exon8}$ KO mouse and *wfs1ab*^{KO} zebrafish [71]. Using overexpression of S1R or the potent prototypic S1R agonist PRE-084 [72,73], we demonstrated that activating S1R corrected the cellular deficits in WS1 patients' fibroblasts (calcium transfer, mitochondrial function, auto- and mitophagy), in *Wfs1*$^{\Delta exon8}$ KO mouse (cognitive impairment, increase anxiety) and in *wfs1ab*^{KO} zebrafish (hyperlocomotion) [71]. These convincing data have high potential to open up a new avenue for an efficient treatment of WS in the future.

Overall, these data suggested that WS represents a pathology of the MAMs that we named MAMopathy and there is a significant impact of wolframin and CISD2 on the MAM function involving the ER stress, calcium signaling, mitophagy and ER-mitochondria tethering (Fig. 2).

3. MAMs in familial Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms bradykinesia, tremor, and rigidity due to the progressive loss of dopaminergic (DA) neurons in the substantia nigra region of the midbrain [74,75]. The PD etiology is largely unknown but evidences from PD patients, postmortem studies and PD linked gene mutations suggest the involvement of mitochondrial dysfunction, inflammation, impaired autophagy, proteasome system and oxidative stress as potential PD mechanisms [74,76,77]. Emerging evidence suggests that disruption of MAM integrity and function may contribute to the development of PD. This is because MAMs play crucial roles in mitochondrial homeostasis (including morphology, dynamics, function and degradation), autophagy, Ca^{2+} homeostasis, apoptosis and inflammation [29] (Fig. 3).

The majority of PD cases is sporadic, however, less than 10 % of cases are familial PD cases which are caused by mutations in >22 genes [75,78,79]. These genes can be grouped based on their inheritance into autosomal recessive and autosomal dominant genes. Mutations in autosomal recessive (AR) genes such as *PINK1, Parkin, DJ-1* and *ATP13A2,* cause early-onset PD (EOPD, onset before 50 years of age) [80]. Interestingly, all of them encode proteins involved in mitochondrial function and quality control [77,81]. Moreover, several of these genes are found to play important roles in MAM formation and function (Fig. 3). PINK1 (a mitochondrial serine/threonine kinase) and Parkin (an E3 ligase) play crucial roles in mitochondrial quality control. In detail, dissipation of mitochondrial membrane potential [82] or mitochondrial protein aggregation [83,84] prevents the mitochondrial import of PINK1 which stabilizes and gets activated on the mitochondrial surface [85–89]. Activated PINK1 then phosphorylates ubiquitin and Parkin leading accumulation of Parkin in mitochondria [90–95]. Following mitochondrial translocation, Parkin ubiquitinates a variety of OMM substrates such as Mfn1/2 [96–98], Miro1/2 [99,100], VDAC [24,101], TOMs [102] and mitochondrial hexokinase [100]. The ubiquitinated OMM substrates are phosphorylated by PINK1 [85,100,103,104] to recruit more Parkin and leading to a multifold increase in ubiquitination through a feed-forward loop [91,105–107]. The decision that ubiquitin decorated mitochondria would undergo mitophagy or not would be regulated by OMM deubiquitinase, USP30 which could deubiquitinate OMM proteins to reverse Parkin-dependent ubiquitination and prevent mitophagy [108]. The persistance of phosphoubiquitin signal on OMM recruits the autophagy receptors optineurin and NDP52, which initiate autophagophore biogenesis to engulfment of the damaged mitochondria [109–111]. Mitochondria trapped by autophagosomes are ultimately degraded by lysosomal enzymes following autophagosome-lysosomal fusion [105,112]. Thus, PINK1/Parkin mediated mitophagy could limit the release of ROS, pro-inflammatory and pro-apoptotic signals from dysfunctional mitochondria by eliminating them and maintain mitochondrial homeostasis. During this process of mitophagy, the relocalization of PINK1 to MAMs has been found to increase the contacts between ER and mitochondria and to promote the formation of autophagosome precursors [113]. Similar to PINK1, Parkin has also been found to exist in MAMs [113] and both of them are found to increase the contacts and communication between ER and mitochondria [113–115]. In fact, Parkin mutation or silencing was found to disrupt the integrity of MAM in human fibroblasts [116]. Whereas overexpression of Parkin could increase contacts as well as communications between ER and mitochondria and augment mitochondrial ATP production in cellular systems [114,115]. Similar to Parkin, the silencing of PINK1 reduced ER-mitochondrial contacts and MAM function [117]. As mentioned above, Parkin ubiquitinates mitochondrial pro-fusion protein Mitofusins pair (Mfn1 and Mfn2) at the onset of mitophagy. Mfn1 was found to be degraded by proteasome following Parkin mediated ubiquitination whereas Mfn2 ubiquitination

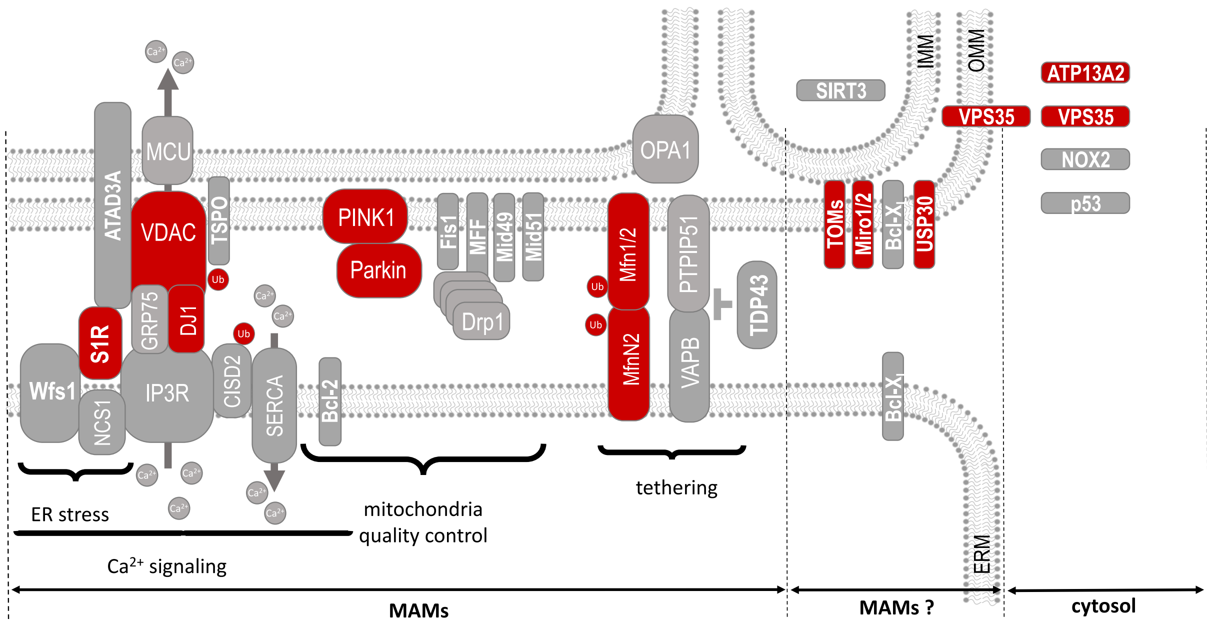

Fig. 3. Highlighted in red: MAM proteins associated with familial Parkinson's disease. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was found to dissociates mitochondria from the ER to promote mitophagy [118]. Moreover a study has shown that the non-ubiquitinatable Mfn2 mutant fails to restore ER-mitochondria physical and functional interaction [116]. These studies suggest the role of Parkin-mediated Mfn2 ubiquitination in maintaining physical and functional integrity of MAMs. Similar to *Parkin and PINK1*, another PD linked protein DJ-1 is found to be located in MAM. DJ-1 may play a key role in IP_3R-GRP75-VDAC tethering protein complex of MAMs as evident from the finding that DJ-1 deficiency disrupts the interactions of IP_3R, GRP75, and VDAC, resulting in the reduction of ER-mitochondrial contacts [20]. Thus, reduction in level of DJ-1 in substantia nigra of PD patients could lead to the disruption of IP_3R-GRP75-VDAC tethering protein complex, which could result in the disabled Ca^{2+} crosstalk and reduced ATP production. Eventually these detrimental changes could result in mitochondrial structure abnormalities and dysfunction. In addition to autosomal recessive genes, autosomal dominant PD genes are also associated with MAMs, as well as mitochondrial and ER function. For instance, LRRK2, the most commonly mutated gene linked to late-onset PD, is involved in PINK1/Parkin mitophagy and mitochondrial trafficking [119,120]. Similarly, mutations in other autosomal dominant PD gene *SNCA* encoding for the major component of Lewy bodies, α-synuclein or in *VPS35* delays or impairs mitophagy [121–123]. Beside the role in mitophagy, α-synuclein has been found to influence ER-mitochondrial contacts and MAM functions due to its high abundance in MAMs [124]. Moreover, α-synuclein mutations reduce in the association of tethering protein in MAM directly [125] or via interacting with VAPB that disrupts the VAPB-PTPIP51 interaction [126].These studies highlight the importance of PD-linked genes in MAM formation and function. Disruption of them could collectively lead to the pathogenesis of familial PD.

Enhancing PINK1/Parkin mitophagy is an attractive strategy to prevent DA neuron loss in PD patients, not only in cases involving PINK1/Parkin loss but also in sporadic PD. In this direction, carnosic acid (CA) from rosemary has been shown to activate PINK1/Parkin-mediated mitophagy and prevents the neurotoxicity of 6-hydroxydopamine (6-OHDA) in SH-SY5Y cells [127]. Not only in cellular, also in animal PD model (MPP^+/MPTP-induced) the enhancement of PINK1/Parkin-mediated mitophagy by salidroside provided neuroprotection [128]. Besides them two related compounds T0466 and T0467 stimulated PINK1-Parkin dependent mitophagy in iPS-derived dopaminergic neurons without depolarizing mitochondria [129]. Moreover, these compounds improved the motor defects, aggregated mitochondrial morphology and decreased ATP production caused by reduced PINK1 activity in the *Drosophila* PINK1 deficient model [129].

Parkin is a RING-Between-RING E3 ubiquitin ligase that is conformationally autoinhibited under basal conditions [130]. Small molecules like BIO-2007818 can directly activate auto-inhibited Parkin in the presence of phospho-ubiquitin. However, it does not enhance the Parkin translocation rate to mitochondria and mitophagy [131]. The Parkin recruitment to damaged mitochondria and their lysosomal removal can be enhanced by Rho-associated Protein Kinase 2 (ROCK2) inhibitors [132]. These ROCK2 inhibitors have demonstrated neuroprotective effects in the paraquat flies model of parkinsonism [132].

Similar to Parkin, PINK1 could be activated by two major classes of activators first KTP (kinetin triphosphate) and its analogues [133,134], and the second class is niclosamide and its analogues [135]. KTP (analogue of ATP) enhances the PINK1 activity (wild type and some defective mutants) and the Parkin translocation to mitochondria [133]. Moreover, it has been demonstrated to rescue defects in mitochondrial morphology and motor deficits in *PINK1*-knockdown flies [129,133,134,136]. However, in PINK1 deficient rats, the effect of KTP was inconclusive because *PINK1* knockout rats did not exhibit neuronal degeneration [137]. The other type of PINK1 activator niclosamide, an oral antihelminthic drug, induces reversible mitochondrial depolarisation to enhance PINK1 stabilization and activity in cultured neurons [135,138].

As mentioned above, USP30 antagonizes mitophagy by removing ubiquitin chains from ubiquitinated OMM substrates of Parkin [108,139,140]. Hence inhibition of USP30 has the potential to up-regulate mitophagy. In fact, pharmacological or genetic inhibition of USP30 have been shown to enhance mitophagy in neuroblastoma SHSY5Y cell line, iPSC-derived dopaminergic (DA) neurons, in patient derived fibroblasts harboring Parkin mutations and in Parkin- or PINK1-deficient flies [108,141]. Many highly selective USP30 inhibitors are described to potentiate mitophagy such as FT3967385, CMPD-39 and a peptide (Q14) derived from USP30 transmembrane domain [142–145]. The major problem in targeting deubiquitinating enzymes (USP30) is their physiological importance in protein import and their quality control at OMM [141,146,147]. However, USP30 inhibition remains an additional strategy to stimulate PINK1/Parkin mitophagy.

Very recently, it was reported that the number of 20 nm ER-mitochondrial contact sites was severely reduced in astrocytes derived from PD patients [10]. As a consequence, ER-originating Ca^{2+} fluxes that actually reach the mitochondria were severely impaired. Interestingly, enhancing ER-mitochondrial contact sites at a 20 nm distance using molecular rules could rescue mitochondrial Ca^{2+} uptake in PD-derived astrocytes.

Finally, activation of S1R has also been reported to protect dopaminergic neurons in experimental Parkinsonism. First, PRE-084 improved the spontaneous forelimb use of mice after intrastriatal treatment with 6-hydroxydopamine [148]. The behavioural recovery was paralleled by an increased density of dopaminergic fibres in the most denervated striatal regions, by a modest recovery of dopamine levels, and by an upregulation of BDNF and GDNF levels and their Erk1/2 and Akt effector pathways. Second, treatment with PRE-084 reduced loss of dopamine neurons, restored motor ability and MPTP-induced damage to mitophagy activity in the SNc of PD-like mice [149]. Additionally, S1R knockdown in SH-SY5Y dopaminergic cells inhibited mitophagy and enhanced MPP+ neurotoxicity, whereas application of the S1R selective agonist (+)-SKF-10,047 promoted clearance of damaged mitochondria [149].

4. MAMs in Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is a disease affecting motor neurons (MNs) and is caused by genetic mutations in 5–10 % of all cases [150]. Accumulating evidence highlights that the MAMs harbor a multifaceted dynamic interplay among several key proteins affecting some of the most relevant pathological mechanisms identified in both familial and sporadic ALS, including altered Ca^{2+} homeostasis, mitochondrial dysfunction, response to ER-stress and protein misfolding (Fig. 4). S1R plays a central role in these processes. In fact, the inactivation of S1R causes alterations of MAMs and intracellular calcium signaling in MNs in vitro, leading to ER stress and defects in mitochondrial dynamics and transport [151]. Knockout of S1R in transgenic SOD1.G93A mouse model of ALS exacerbated the clinical progression of symptoms, further highlighting the crucial protective role of S1R for MNs in the disease process [152].

Alterations of S1R protein levels and subcellular distribution were also highlighted in MNs from the lumbar spinal cord of both sporadic and familial (ALS-8, VAPB mutant) ALS patients not linked to *C9orf72*, supporting the crucial role of S1R in ALS pathophysiology [153]. In 2011, a recessive missense mutation of S1R (E102Q) was found in a family affected by a juvenile form of ALS [154]. Expression of human mutant S1R.E102Q in a MN cell line determined the aberrant subcellular distribution of S1R and increased susceptibility to ER-stress induced death, suggesting that mutant S1R may lose a protective function important for MN survival.

Few juvenile cases of ALS have been associated to a missense mutation (c.304G>C, p.E102Q) and a frameshift mutation (c.283dupC, p.L95fs) in S1R [154,155]. While expression of wild-type S1R in MCF-7 cell culture led to the activation of IP_3R-mediated Ca^{2+} release from the ER, E102Q-mutant S1R induced an impairment of Ca^{2+} release [156]. Accordingly, the eye malformation due to the presence of E102Q-mutant S1R in *Drosophila* is rescued by overexpression of the wild-type but not mutant IP_3R [157]. This underlies the importance of the interaction between S1R and IP_3R-mediated calcium signaling.

It is noteworthy that mutations in VAPB are linked to familial ALS [158]. Mutations in VAPB enhanced its binding to PTP51 and its accumulation at MAM [159]. This led to increased release of calcium from ER which had damaging consequences by elevating calcium levels in mitochondria or by altering mitochondrial transport through Miro1 [159,160]. In addition, numerous studies have reported a trend toward mitochondrial fragmentation in ALS, suggesting an alteration of the mitochondrial fusion/fission balance [161]. In most cases, this may result from a misregulation of key proteins regulating mitochondrial dynamics. Indeed, expression levels of the profusion genes, Mfns and OPA1, were reported to be reduced in ALS patients or models [162–165] while phosphorylation of the pro-fission protein Drp1 was found increased [162,166].

Tar-DNA binding protein (TDP43) is a key ALS gene involved in familial cases but also in the majority of sporadic cases [167]. Mutant TDP43 altered the VAPB-PTPIP51 interaction and thereby ER-mitochondria association [168]. Moreover, since Mfns were found to be downregulated in ALS patients [163] as well as in SOD1 mice, TDP43 mice and *Drosophila* models [163,165,166], it is expected to perturb ER-mitochondria contacts [21]. Overexpression of Fused in Sarcoma (FUS), whose mutations cause familial ALS, also disrupted the VAPB–PTPIP51 interaction and ER–mitochondria tethering in mice [168]. Interestingly, a screen for MAM disruption using MAMtrakers on 21 ALS-causative genes allowed to identify 16 positive genes in cultured cells [169]. Among others, we can cite SOD1, TDP43, T-cell-restricted intracellular

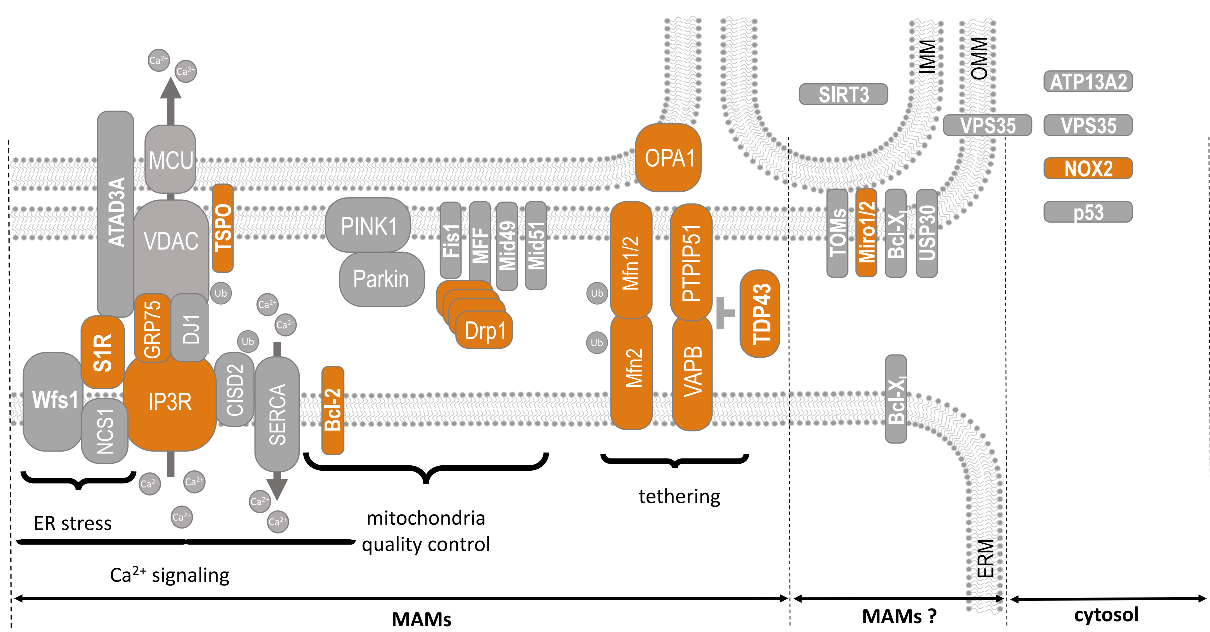

Fig. 4. Highlighted in orange: MAM proteins associated with Amyotropic lateral sclerosis.

antigen-1 (TIA1), TATA-box binding protein associated factor 15 (TAF15), factor-induced gene 4 (FIG4), charged multivesicular body protein 2B (CHMP2B), p62/sequestosome-1, tubulin alpha-4A chain (TUBA4A), coiled-coil-helix-coiled-coil-helix domain containing protein 10 (CHCHD10), matrin 3, valosin-containing protein (VCP), profilin 1 and S1R [169].Concerning Miro1, reduced levels were observed in the spinal cord of ALS patients and mouse models expressing mutant SOD1 or TDP43 [170,171]. Reduced mitochondrial membrane potential, altered calcium homeostasis, reduced levels of the antiapoptotic protein Bcl-2, and increased ER stress were reported in MNs derived from iPSCs of ALS patients carrying the hexanucleotide expansion in C9Orf72 (which accounts for up to 40 % of familial cases and 7 % of sporadic ALS in Europe) [172].

S1R was described to reduce ER stress by interacting with three key proteins of the UPR: BIP, PERK and IRE1 [11,173,174]. Moreover, the direct interaction between ATF4 and the 5′ flanking region of the S1R gene further supports the evidence of the close link between S1R and ER stress response [175]. Indeed, ATF4 enhanced S1R expression during ER stress, thus promoting the protective effect of S1R on ER stress [175] Conversely, a downregulation of S1R was reported in lumbar spinal cord specimens from sporadic ALS patients and this was accompanied by increased levels of the ER stress marker Bip/GRP78 [153]. These two events are linked since the S1R knockdown in cell culture generated not only an accumulation of misfolded protein with alteration of the ER structure but also an increased level of ER stress markers [153]. Moreover, the mutation E102Q in S1R was shown to favor its aggregation and accumulation into ER and promote ER stress in lymphoblastoid cells from E102Q-SIR fALS patients [156]. Altogether these observations indicate that misexpression or mislocalization of S1R seems to result in ER stress.

Interestingly, it was recently observed that C9ORF72 patient-derived MNs increase the expression of GRP75 as an early compensatory mechanism in response to ER stress. The transient upregulation of GRP75 levels enhances the ER-mitochondrial tethering and boosts mitochondrial function to support cellular bioenergetics during the initial stage of disease. Over time, the accumulation of dipeptide-repeats (such as polyAG), induced by C9ORF72 hexanucleotide expansion (HRE), determines the formation of inclusions that sequester GRP75 thereby affecting this neuroprotective pathway [176].

MAMs in glial cells contain critical proteins implicated in neuroinflammation and could be regarded as a hub modulating several pathways critically implicated in reactive gliosis. Importantly, TSPO, a transmembrane protein localized in the outer mitochondrial membrane, was confirmed to be present also at MAMs [177]. TSPO integrates several cellular response pathways such as (i) regulation of mitochondria cholesterol uptake [178]; (ii) to interaction with the voltage-dependent anion channel (VDAC) [179]; and (iii) modulation of the membrane permeability transition pore (mPTP), [180] with impact on cellular survival and proliferation. At the molecular level, TSPO expression is directly modulated by changes in reactive oxygen species (ROS). In fact, the Tspo promoter contains several ROS-sensitive elements, such as AP1, ERK1/2 and PKCε, that can induce TSPO expression in a ROS dependent manner [181]. TSPO overexpression, in turn, is associated with ROS overproduction and mitophagy inhibition. Also, the proinflammatory cytokines IL-1β and TNF-α are involved in this process, suggesting that a pro-inflammatory environment contributes to TSPO upregulation [182]. This represents an adaptive change that, in the short term, allows a rewiring of cellular metabolism to survive and counteract extracellular stressors. However, over time, during chronic neurodegeneration, a positive feedback loop eventually takes place whereby ROS and stressors induce TSPO expression, and this phenomenon leads to further ROS production, impaired mitophagy and accumulation of cumulative mitochondrial damage [181].

Interestingly, an association of TSPO with the two principal subunits of NADPH oxidase 2 (NOX2), gp91^{phox} and p22^{phox}, at MAMs was demonstrated in microglia cells [183]. NOX2 is a multi-subunit enzyme complex, involved in redox stress and induction of pro-inflammatory cytokines [184]. Among the four NOX isoforms, NOX2 expression levels were found significantly increased in the spinal cord of SOD1. G93A mice already at the pre-symptomatic stage for all the duration of the disease [185–187]. This finding was confirmed also in TDP43^{Q331K} and FUS/TLS transgenic mice and in post-mortem samples from ALS patients [187]. Lower NOX2 activity correlates with increased survival in ALS patients [188], suggesting that NOX2 may be a crucial disease modifier not only for SOD1-related ALS cases but also for sALS. TSPO seems to modulate ROS production via NOX2 through the interaction with the ER-resident NOX2 subunit gp91^{phox} in primary microglia and this interaction is increased also in the brain of the Sandhoff mouse model of neurodegeneration [183]. In support of this evidence, the responses induced in primary microglia by TSPO ligands PK11195 and Ro5–4864 were prevented in the presence of NOX2 inhibitors [189].

To date the two medications for ALS that were approved by FDA are the glutamate-modulating drug, Riluzole, and the anti-oxidative stress compound, Edaravone. However, their efficiency is quite limited, and they do not halt the progression of the disease. Thanks to previous studies, S1R has emerged as a key therapeutic target to ameliorate ER stress response and Ca^{2+} exchanges, two key physiological events impaired in ALS pathology [190]. So far, the therapeutic efficiency of S1R agonists has been mainly reported on SOD1 ALS mice. Administration of the S1R agonists PRE-084, SA4503, Pridopidine or EST79232 ameliorated motor neuron survival, motor performance or extended survival of SOD1 mice [191–194]. In 2014, PRE-084 neuroprotective and immunomodulatory effects were reported in the wobbler mouse model of motor neuron degeneration, supporting the therapeutic potential of S1R agonists also for ALS not linked to SOD1 mutation [195]. More recently, PRE-084 treatment was shown to be efficient in rescuing the motor phenotype of zebrafish larvae expressing mutant TDP43 [196]. PRE-084 enhanced ATF4 signaling pathway, oxidative stress defense and mitochondrial maximal respiration in TDP43 zebrafish larvae [196]. Although the translation of this observation on TDP43 mouse models is still necessary, these data further support the therapeutic role of S1R modulation also for ALS linked to TDP43. Moreover, treatment of NSC34 cells expressing the C9ORF72 HRE with pridopidine reinforces the association between S1R and the nucleoporin POM121, thereby enabling the nuclear translocation of TFEB and the induction of autophagy as a neuroprotective response [197]. Of note, pridopidine is currently in phase 2 clinical development in ALS [198]. In addition, olesoxime, a cholesterol-based compound that targets the mPTP (by interacting with TSPO and VDAC) [199], prevents the release of apoptotic factors from mitochondria, improved motor performance, and delayed the onset of disease in the SOD1.G93A mouse model [200]. Further than TSPO, S1R is an interactor of VDAC. S1R is detected not only in neurons but also in glial cells [201], including astrocytes [177,201] and microglia cells [201,202]. In line with these observations, when S1R was studied in a mouse model of motor neuron degeneration not linked to SOD1 mutation, the wobbler mouse, it was observed that with the progression of the pathology S1Rs become highly expressed in astrocytes and in activated microglia/macrophages [195]. Indeed, the increased motor neuronal survival reported in ALS mice treated with S1R agonists [191] was accompanied by a reduction of reactive gliosis, the decrease of some pro-inflammatory cytokines such as IL-1β, and the induction of BDNF [195]. In line with these observations, it was reported that the neuroprotective agent afobazole, acting on S1R in microglial cell cultures, decreases microglial response to ATP and improves microglial cell survival during and after ischemia [203]. Studies on zebrafish model of acute brain damage confirmed that agonists of S1R modulate microglia reactivity allowing re-gaining of a physiological de-activated phenotype [204]. Thus, the neuroprotective effects of S1R agonists observed in ALS mouse models could be the result of a synergic action exerted at the MAMs both in MNs and in glial cells [205–207].

5. MAMs in ATAD3A-related pathologies

Harel-Yoon syndrome, identified in 2016 [208], is a rare early-onset ND caused by pathogenic variants of ATAD3A, an AAA protease spanning the inner and outer mitochondrial membrane that binds nucleoids in the mitochondrial matrix and interacts with other proteins in cytoplasm. ATAD3A plays a role in facilitating mitochondrial dynamics, suppression of mitophagy, and in trafficking of cholesterol [209], where all these processes are promoted by proteins enriched in MAMs. There is no effective treatment for HYS and the modulation on ATAD3A function via MAM proteins may represent an effective therapeutic strategy in the future. The phenotype-genotype spectrum in *ATAD3A*-related disorders ranges from biallelic deletions with a neonatal-lethal phenotype, to monoallelic single nucleotide variants leading to complicated hereditary spastic paraplegia [208,210,211]. Biallelic deletions are mediated by non-allelic homologous recombination between the three paralogs at the *ATAD3* locus, and result in severe brain malformations, ophthalmological abnormalities, cardiomyopathy and respiratory failure after birth [208,212,213]. The reciprocal duplication leads to a similar neonatal-lethal phenotype, presumably via a dominant-negative effect [214,215]. A recurrent monoallelic single nucleotide variant (NM_001170535.1: c.1582C>T p.Arg528Trp) has been identified in numerous families, and causes a mitochondrial-like phenotype including optic atrophy, cardiomyopathy, neuropathy and developmental delay [208]. Finally, biallelic hypomorphic variants lead to congenital cataract, cerebellar hypoplasia and epilepsy. The effects of novel variants in *ATAD3A* may be difficult to predict; interpretation may be facilitated by modeling in *Drosophila* [216] or other in vivo or in vitro models.

ATAD3A is a nuclear-encoded mitochondrial membrane protein that belongs to the AAA+-ATPase protein family. The gene is ubiquitously expressed and has two paralogs: *ATAD3B* which is expressed in embryonic stem cells and re-expresses in cancer cells, and *ATA3C* which is a pseudogene [217,218]. ATAD3A has a unique structure with a C-terminus that includes a conserved ATPase and is located in the mitochondrial matrix and an N-terminus associated with the MAMs via its proline-rich motif [219–221].

Integrated omics and high-resolution microscopy identified that ATAD3A is evenly distributed across the mitochondrial network, and physically connects the outer and inner mitochondrial membranes [222]. ATAD3 was shown by global mass spectrometry-based proteomic analysis to be enriched in ER-mitochondrial junctions termed mitochondria-associated membranes (MAMs) [223] (Fig. 5).

ATAD3A has been reported to be involved in the control of mitochondrial dynamics, which is mediated by fission and fusion of the mitochondria. There is evidence for the interaction of ATAD3A with multiple proteins involved in both fission and fusion processes. Interaction of ATAD3A with fusion proteins, Mfn2 and OPA1, and with the fission protein, Drp1, was revealed in human lung adenocarcinoma cell lines by co-immunoprecipitation [224] and also in mice [225]. Moreover, ATAD3A was found to interact with fission proteins which are located in the outer membrane (MFF) and in the mitochondrial matrix (TFAM) beyond the inner membrane of the mitochondria [226].

In the heart, ATAD3A was found to interact with the crucial regulator of MAMs, the IP_3R1-GRP75-VDAC1 complex. The IP_3R1-GRP75-VDAC1 complex constitutes a crucial channel for calcium flux from the ER to the mitochondria in the heart. ATAD3A in its monomeric form interacts with the IP_3R1-GRP75-VDAC1 complex, and this interaction leads to mitochondrial calcium overload and dysfunction The SIRT3-ATAD3A axis promotes ATAD3A oligomerization and by this controls the calcium flux in the heart [227]. ATAD3A interaction with S1R is required for maintaining MAM integrity (Fig. 5). S1R was found to keep ATAD3A in its monomer form; disruption of this interaction may result in ATAD3A oligomerization and accumulation, which can disrupt MAM integrity and lead to neurological pathogenesis [228,229]. In Huntington's disease (HD) mutant cells showed a higher abundance of ATAD3A in the contact sites between the outer and inner membranes [230]. ATAD3A oligomerization was also increased at the MAMs in various Alzheimer's disease (AD) models. This aberrant oligomerization of ATAD3A induced AD-like hyperconnectivity of MAMs and impaired neuronal cholesterol turnover by inhibiting CYP46A1 (Cytochrome P450 Family 46 Subfamily A Member 1) gene expression [229]. Presented discrepancies stated in this paragraph regarding ATAD3A oligomerization may be tissue-dependent (cardiac vs neuronal). Moreover, the impact of ATAD3A on MAM integrity and mitochondrial function is critically dependent on its oligomerization levels with a delicate optimum. In case of low ATAD3A oligomerization, the MAMs are destabilized, thereby causing Ca^{2+} overload and mitochondrial dysfunction. Yet, also in case of excessive ATAD3A oligomerization, MAM integrity is disrupting, leading to neurological disease. Overall, balancing the level

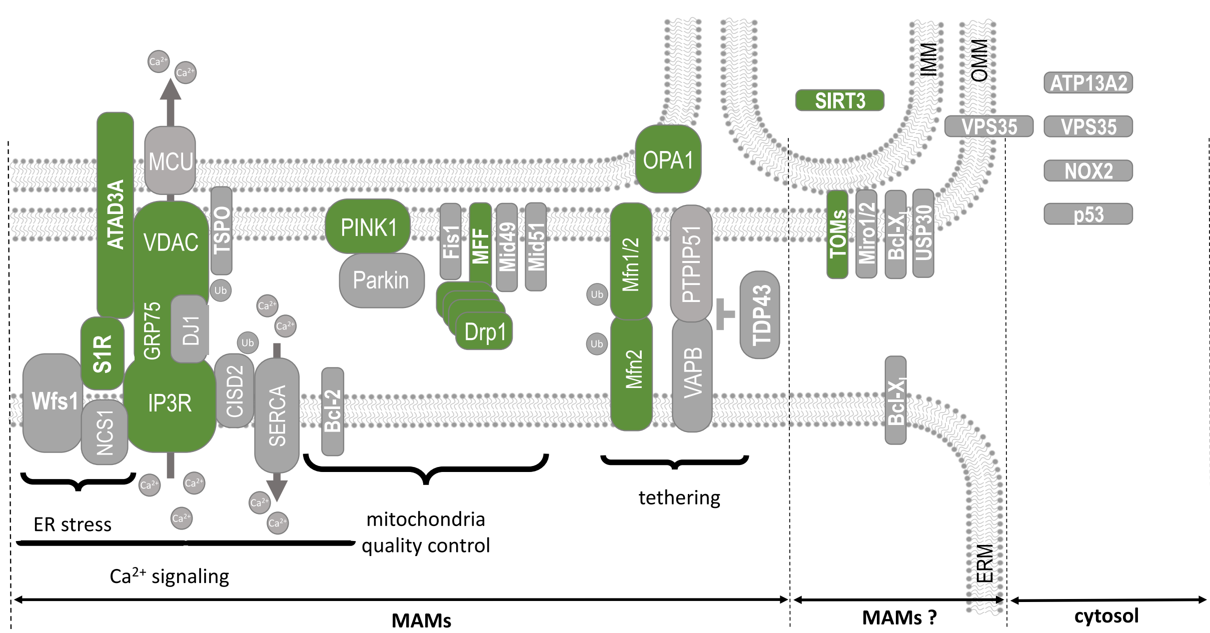

Fig. 5. Highlighted in green: MAM proteins associated with ATAD3A related pathologies. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of ATAD3A oligomerization is essential for MAM functioning; however, its behaviour is complex and requires further research.

As a member of the MAM, *ATAD3A* is also related to the ER and ER stress. ATAD3A interacts with PERK in a manner which reduces signaling to eIF2α during ER stress in the MAM [231]. It also provides chemoresistance in colorectal cancer through interaction with GRP78, leading to ER-stress suppression [232].

ATAD3A affects ubiquitination pathways, mitophagy and apoptosis. It regulates mitophagy by reducing PINK1 stability [233,234]. Deletion of Atad3a (the mouse ortholog) in hematopoietic mice cells resulted in overactive mitophagy [234]; the protein was shown to assist PINKs1 transportation through interaction with Tom40 and Tim23. In its absence PINK1 accumulates, thus hyper-activating mitophagy. Through these pathways, *ATAD3A* also has an association with cancer: high *ATAD3A* expression is correlated with poor prognosis and is found in various tumors [235]; it was found to promote metastasis in several cancers including uterine cervical cancer [236], lung adenocarcinoma (LADC) [224], prostate [237] and more. In prostate cancer, it was shown to be through apoptosis inhibition due to prostate-specific antigen secretion. In breast cancer, *ATAD3A* inhibits PINK1 and by this prevents PD-L1 mitochondrial distribution, causing tumor resistance [238].

In general, *ATAD3A*-related treatment can be divided into two approaches: either for *ATAD3A*-associated disorders caused by pathogenic variants in the gene (missense variants, deletions or duplications), or for WT *ATAD3A* which affects pathologies through its overexpression or oligomerization. Currently, there is no cure for *ATAD3A*-related monogenic disorders from the first group. As for the other group, there have been trials showing improvement by targeting *ATAD3A*. In cancer, inhibition of *ATAD3A* reduced drug resistance: in LADC cells, blocking the phosphorylations of ATAD3A by protein kinase C caused the destabilization of ATAD3A [224]. Resveratol was shown to reduce *ATAD3A* expression in uterine cervical cancer, increasing autophagy and reducing drug resistance [236]. In neuronal models for Alzheimer's disease, DA1 treatment restored CYP46A1 levels, MAM integrity and cholesterol metabolism. It suppressed APP processing, mitigated synaptic loss, and ultimately reduced AD-associated neuropathology and cognitive deficits, similar to the effects of *ATAD3A* knockout [229]. Blocking the Drp1/ATAD3A interaction using DA1 also abolished ATAD3A oligomerization, suppressed mitochondrial fragmentation and mtDNA lesion, and reduced bioenergetic deficits and cell death in HD mouse- and patient-derived cells [230]. Notably, ATAD3A is dosage-sensitive [220]. Pathologies can arise from either loss-of-function or dominant-negative variants, but also from high expression of the WT protein. This has implications on therapy, as ATAD3A cannot be completely knocked-out nor overexpressed.

6. MAMs in cancer

The involvement of MAMs in cancer is well documented, with many MAM-associated proteins, such as those in the IP_3R-GRP75-VDAC pathway, as well as those related to ER stress, ER-mitochondria tethering, and mitochondria quality control, playing significant roles in the onset and progression of the disease [30,239–241].

The Ca^{2+} signals at mitochondria-associated ER membranes (MAMs) in cancer cells can serve a dual role to contribute to the cancer hallmarks (Fig. 6). By modulating the ability of IP_3Rs to transfer Ca^{2+} into mitochondria, cancer cell growth and proliferation can be impacted. On the one hand, basal IP_3R function is essential to sustain cancer survival by fueling mitochondrial bio-energetics and nucleotide biosynthesis [242,243]. On the other hand, IP_3Rs can evoke cancer cell death through mitochondrial Ca^{2+} overload. The B cell lymphoma 2 (Bcl-2) protein family consisting of both pro- and antiapoptotic members, also resides at the ER and ER-mitochondrial contact sites, where they can directly impact the Ca^{2+}-flux properties of IP_3Rs in cancer through their non-canonical functions [244]. Antiapoptotic members like Bcl-2 and Bcl-X_L play a major role in this regulation. These proteins can suppress IP_3R function, preventing mitochondrial Ca^{2+} overload and cell death (such as Bcl-2) or enhance basal IP_3R function, promoting mitochondrial function and bio-energetics (such as Bcl-X_L) [245–247]. In addition to anti-apoptotic Bcl-2 family members, pro-apoptotic Bcl-2 members have also been implicated in controlling IP_3R function. The multi-domain protein Bok emerged as a prominent IP_3R-associated protein. IP_3Rs and Bok mutually impact each other's stability [248,249], whereby Bok binding to the coupling region of IP_3Rs prevents proteolytic cleavage of IP_3Rs [248] and Bok degradation [249]. Bok, similarly to Bax and Bak, can mediate mitochondrial outer membrane permeabilization (MOMP) by forming oligomeric pores [250]. More recently, Bok was found to reside at the MAMs, thereby enhancing ER-mitochondrial Ca^{2+} transfer in two ways: (i) by promoting ER-mitochondrial contact sites; and (ii) by boosting IP_3R-mediated Ca^{2+} release [251]. Both Bok functions appear

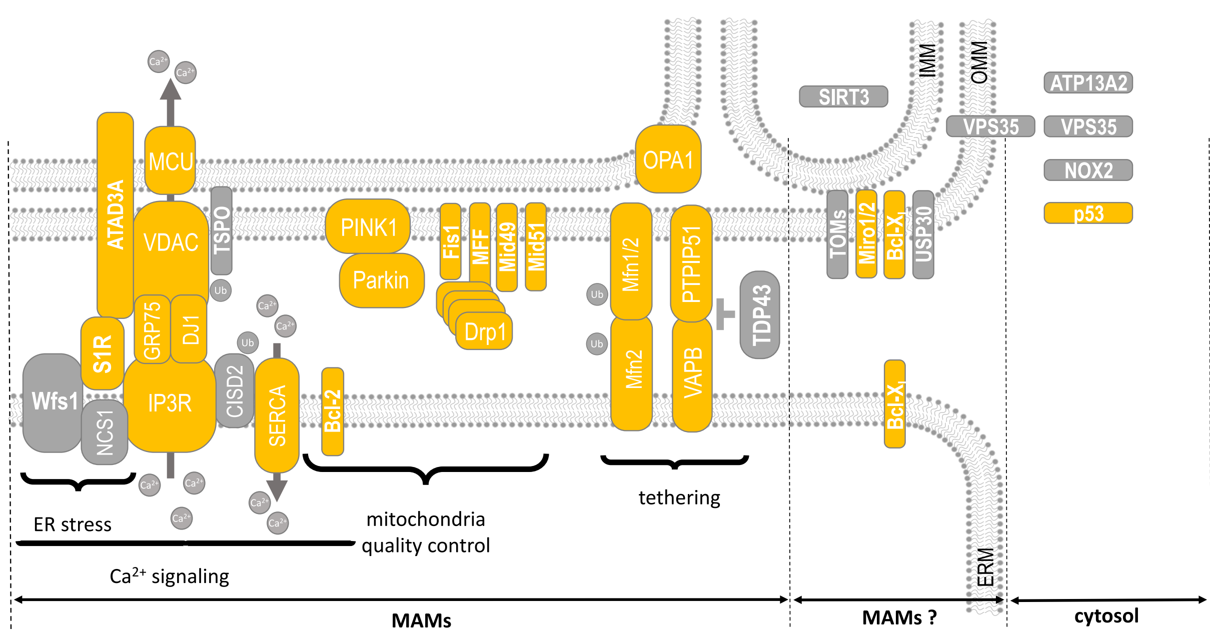

Fig. 6. Highlighted in yellow: MAM proteins associated with cancer. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

necessary for ER-mitochondrial Ca^{2+} transfer, as ER-mitochondrial linkers or a Bok mutant deficient in IP_3R binding can restore ER-mitochondrial proximity, they do fail to restore Ca^{2+} transfer and apoptosis in Bok-deficient cells.

The other parts of the IP_3R-GRP75-VDAC1-MCU pathway can also be dysregulated in cancer cells (Fig. 6). Observations in chronic lymphocytic leukemia B cells showed that peptide inhibition of the VDAC1-hexokinase isoform 2 interaction at MAMs causes mitochondrial Ca^{2+} overload, which results in cell death [252,253]. The previously mentioned Bcl-2 family not only acts on IP_3R but also influences VDAC1 activity. Bcl-X_L can, via its BH4 domain, interact with VDAC1 and cause inhibition. As a result, mitochondrial calcium influx is reduced, protecting cells from apoptosis [245]. Another Bcl-2 family member, Mcl-1, on the other hand increases mitochondrial calcium levels through its interaction with VDAC1. Mcl-1 is frequently upregulated in NSCLC where it causes Ca^{2+} dependent ROS production enhancing cancer cell migration [254]. The calcium import into the mitochondrial lumen can be further regulated via the MCU, a protein complex essential to transport Ca^{2+} over the IMM. Ovarian cancer cell lines show overexpression of one member of this complex, MICU1, acting as the gatekeeper for mitochondrial Ca^{2+} uptake. This can lead to chemoresistance since a higher threshold for Ca^{2+} uptake needs to be overcome. In vivo, MICU1 silencing resulted in inhibited tumor growth [255,256]. Transglutaminase type 2 (TG2) functions as a scaffold in MAM formation through its interaction with GRP75. TG2 is responsible for activating several oncogenic pathways implicated in cancer progression. While there is consensus that TG2 promotes cancer cell growth, the underlying mechanisms and function of the protein remain unclear [257]. The absence of TG2 reduces MAM formation and ER-mitochondrial Ca^{2+} flux, while also altering MAM architecture. As a compensatory mechanism, the IP_3R3-GRP75 interaction is strengthened [258].

One way by which oncogenes and tumor suppressors can directly impact the Ca^{2+}-flux properties of IP_3Rs is through post-translational modifications. For instance, the tumor suppressor promyelocytic leukemia (PML) resides at the MAMs and recruits protein phosphatase 2A (PP2A), which dephosphorylates protein kinase B (PKB/Akt), a tumor-promoting kinase stimulated by PIP3 that phosphorylates IP_3R3 and dampens Ca^{2+} flux through the channel. As a consequence, in cells containing PML, local PKB/Akt activity at MAMs is reduced, thereby reducing PKB/Akt-mediated IP_3R3 phosphorylation with subsequent increase in ER-mitochondrial Ca^{2+} transfer [259]. PP2A is not the only phosphatase controlling IP_3R function, as also phosphatase and tensin homolog (PTEN), a major tumor suppressor best known for its PIP3 lipid phosphatase actions, acts as a protein phosphatase dephosphorylating IP_3Rs. As such, PTEN helps to sustain pro-apoptotic IP_3R activity, particularly at ER-mitochondrial contact sites [260].

Oncogenes or tumor suppressors acting on IP_3R to alter apoptotic susceptibility directly rely on the Ca^{2+} levels in the ER Ca^{2+} stores. Hence, regulation of the IP_3R Ca^{2+} flux can also be performed indirectly at the level of the ER Ca^{2+}-store content itself. An example is tumor suppressor p53, which has a non-nuclear function at the level of MAMs [239]. During stress situations, p53 stimulates SERCA to take up Ca^{2+}, resulting in increased ER Ca^{2+}-store content and consequent proapoptotic ER-mitochondrial Ca^{2+} fluxes. In cancer cells with mutant or absent p53, SERCA will not be activated to elevate ER Ca^{2+} levels, preventing proapoptotic fluxes and causing further progression of cancer [261]. ER-released Ca^{2+} can also still be taken up by SERCA locally present at the MAMs. Their activity is regulated by thioredoxin-related transmembrane protein 1 (TMX1). When SERCA activity is high, as a result of low TMX1 levels, the mitochondrial Ca^{2+} flux will be reduced causing tumor growth and chemoresistance [262]. However, different studies suggest that cancer cells may instead benefit from high TMX1 (and TMX3) levels. It is therefore always important to keep the specific cellular context in mind when considering the effect of a protein in cancer, with the dual role of TMX1 being a great example of this. Melanoma with upregulated TMX1 and TMX3 results in the activation of calcineurin and consequently the NFAT pathway, driving cell proliferation. Knockdown of TMX1 and TMX3 causes an increase in Nox4-derived ROS which inhibits the NFAT pathway and reduces growth and proliferation [263,264].

Other mechanism through which cells can acquire the hallmarks of cancer, besides acting directly on the IP_3R-GRP75-VDAC1-MCU pathway, is by increasing the ER-mitochondrial distance. Certain spacers such as FATE1 [265] can be upregulated in cancer resulting in increased MAM distance. This reduces the risk of mitochondrial Ca^{2+} overload and can lead to chemoresistance [265,266].

Ca^{2+} signaling in cancer cells is subjected to control of the complex regulatory net of posttranscription regulators as microRNAs (miRNAs). These short single-stranded RNAs complementary to the 3′-end or, more rarely, to the 5′-end of mRNAs can act like oncogenes or tumor suppressors affecting the expression of the key components of mechanisms of ER-mitochondrial Ca^{2+} fluxes via MAMs, reflecting tissue specificity and cellular context. Several miRNAs have been identified controlling the expression of the crucial mechanisms of tethering and Ca^{2+} fluxes - IP_3R-GRP75-VDAC1-MCU pathway as well as spacers affecting MAM distance as Mfn1/2 or FATE1. For example, in silico analysis identified five miRNAs: miR-15, miR-17, miR-21, miR-25, and miR-137 that were proposed to target MCU and/or MICU1 in tumor cells. Similarly, in both, human colon and prostate cancer, the down-regulation of MCU protein related to up-regulated miR-25 have been reported and direct binding of miR-25 to the 3' UTR of MCU mRNA has been demonstrated [267,268]. Next, tumor suppressor miR-340 downregulation correlated with increased MCU expression in breast cancer, suggesting a novel mechanism of enhanced glycolysis promoting breast cancer metastasis [269]. In hepatocarcinoma, miR-7 downregulated VDAC1 and consequently proliferation and invasion [270]. In addition, several miRNAs are involved in the modulation of spacers affecting the distance of MAMs. MiR-195 has been described as targeting *MFN2* in breast cancer cells [271], miR-125 controlling *MFN2* in pancreatic cancer cells [272] and miR-761 in hepatocellular cancer cells [273]. All these miRNAs are suppressors modulating the mitochondrial dynamics. These miRNAs are typically downregulated and allow the upregulation of expression of *MFN2* resulting in increased cell migration and invasion. Their ectopic expression downregulates *MFN2* expression and leads to the activation of mitochondria-dependent apoptosis. Similarly, downregulated miR-19b was shown to trigger Mfn1-induced apoptosis [274]. Several miRNAs have been shown to affect mitochondrial dynamics in chemoresistant cancer cells. For example, in gastric and resistant bladder cancers, miR-98 and miR-148a-3p were shown involved in regulation of Drp1 [275,276], in tongue squamous cell carcinoma cisplatin sensitivity was shown to be controlled by miR-483-5p (TSCC)| targeting Fis1 expression through BRCA1–miR-593-5p–mitochondrial fission factor (MFF) axis [267,277].

Next, a growing body of evidence indicates that MAM-related proteins involved in mitochondrial dynamics—specifically those regulating the opposing processes of mitochondrial fission and fusion—exhibit altered expression in cancer. However, likely due to the overlapping roles of these proteins in MAM functions and ER-mitochondria tethering, the effects of these alterations on cancer cell physiology appear to be context-dependent, with divergent outcomes observed even within the same tumor types. For example, reduced expression of OMM fusion-mediating proteins Mfn1/2, which shifts the balance toward more fragmented mitochondria, has been associated with poor prognosis and more aggressive cancer traits in various carcinomas, including breast carcinoma [278,279], colon carcinoma [280], ovarian carcinoma [281], and hepatocellular carcinoma [282–284]. In contrast, studies in lung adenocarcinoma [285,286], melanoma [287], or hepatocellular carcinoma [288] have identified a positive correlation between poor outcomes and the upregulated expression of mitochondrial fusion-related proteins, OPA1 and Mfn1/2. Silencing Mfn1 or OPA1 significantly inhibited liver tumor formation [288], and blocking OPA1 activity by MYLS22, a specific OPA1 inhibitor, impaired growth of drug-resistant breast carcinoma patient-derived xenografts [289].

Nevertheless, enhanced mitochondrial fission phenotypes have been predominantly linked with increased cancer drug resistance, whereas inhibition of mitochondrial fission was shown to re-sensitize cancer cells to chemotherapy [290–294]. Indeed, upregulation of mitochondrial fission mediator Drp1 and its activating phosphorylation at Ser616 is often associated with aggressive cancer traits, driving tumor progression and contributing to poor prognosis in various tumor types [279,283,295–299]. Correspondingly, expression of Drp1 adaptors, such as FIS1 [287,300–302], MFF [302], and MID49/51 [303], appears to promote mitochondrial fission-associated aggressive cancer phenotypes, including metastasis formation. Inhibiting mitochondrial fission by Drp1 depletion was shown to suppress in vivo tumor growth and restore cancer chemosensitivity [279,302,304–307]. Importantly, several studies have identified mitochondrial fission proteins, such as Drp1 or MFF, as therapeutically promising vulnerabilities for suppressing cancer plasticity and targeting cancer stem-like cells in glioblastoma [308] and various carcinomas [309–314].

Recently, both mitochondrial fission and fusion proteins were demonstrated as crucial for compartmentalization of competing metabolic pathways into morphologically distinct mitochondrial populations, allowing cellular adaptation to changing nutrient environments [315]. Thus, it is not surprising that modulating mitochondrial dynamics in favor of mitochondrial fusion in cancer cells may produce effects similar to those attributed to enhanced mitochondrial fission discussed above. Promoting mitochondrial fusion through Drp1 silencing [316], mdivi-1-mediated inhibition of Drp1 activity [317], or knockdown of its adaptor protein FIS1 [277] enhances resistance of carcinoma cells to widely used genotoxic drug cisplatin. Conversely, downregulation of fusion proteins Mfn1/2 [318–320] or OPA1 [285,286,289] have been shown to sensitize cancer cells to DNA-damaging agents or small molecule inhibitors. Additional complexity arises from the interactions of mitochondrial dynamics-related proteins within MAMs, such as in case of Mfn2, which mediates ER-mitochondria tethering. Recently, Çoku et al. showed that depletion of Mfn2 in neuroblastoma cells efficiently reduces total numbers of MAMs and their proximity to mitochondria, mimicking phenotypes observed in cells from relapsed tumors and phenocopying multidrug resistance due to the attenuated MOMP responses [321]. Interestingly, mitochondrial morphology was unchanged in Mfn2-depleted vs. control or therapy-naïve vs. multidrug-resistant neuroblastoma cells [321,322], further suggesting that, in some contexts, alterations in the mitochondrial dynamics machinery may have more significant impact on shaping MAM function than mitochondria themselves.

As described above, MAMs are crucial sites for regulation of mitophagy, a process essential for maintaining mitochondrial homeostasis and effective quality control by removing damaged mitochondrial compartments [323]. PINK1/Parkin-mediated mitophagy is often hijacked by cancer cells, promoting their resistance to chemotherapy. Interestingly, destabilization of MAM resident protein ATAD3A, an upstream negative regulator of PINK1-activated mitophagy, leads to increased breast carcinoma cell growth [324] and promotes resistance to the protein kinase inhibitor sorafenib in hepatocellular carcinoma cells [325]. Conversely, paclitaxel treatment reduced mitophagy flux by stabilizing ATAD3A in breast carcinoma [238], indicating ATAD3A as a promising target to impair viability of cancer cells dependent on enhanced mitophagy. Of note, excessive PINK1/Parkin mitophagy, stimulated by increased Drp1-mediated mitochondrial fission, have also detrimental effects on cancer cell survival [326,327]. Finally, besides their canonical roles in mitochondrial trafficking, mitochondrial Rho GTPases Miro1/2 are emerging as important regulators of ER-mitochondria contacts [328] and mitophagy [28]. Future research should explore how these functions align with the currently prevailing consensus that Miros primarily promote tumor progression [329].

Several clinically used chemotherapeutics induce cell death partly by modulating ER-mitochondrial Ca^{2+} fluxes. For instance, ATO, used to treat acute promyelocytic leukemia patients [330], leads to higher PML-protein levels (in cancer cells often downregulated) at ER mitochondrial contact sites. This results in an increased ER-mitochondrial calcium flux, promoting mitochondrial respiration. Consequently, the pro-survival autophagy pathway gets repressed [331]. Another chemotherapeutic drug is the platinum-based cisplatin, which covalently binds and damages DNA [332]. This drug also affects the ER mitochondrial Ca^{2+} flux by increasing both the number of ER mitochondrial contact sites and the mitochondrial calcium concentration thereby causing apoptosis. To restore cisplatin efficacy in cancer treatment, Bcl-2 inhibitors such as the BH3 mimetic ABT-737 can be applied [333–335]. The SERCA inhibitor thapsigargin could also enhance cisplatin efficiency since cisplatin treatment increases expression levels of Ca^{2+} transport channels as was observed in neuroblastoma cells [336]. Next, adriamycin or doxorubicin are drugs used in cancer therapy that affect ER-mitochondrial Ca^{2+} transfer, making cells more susceptible to apoptosis. By increasing p53-protein levels at the ER and MAMs, adriamycin boosts SERCA activity. This increased SERCA activity enhances ER-mitochondrial calcium signaling leading to apoptosis [261,266,337].

In addition, several types of cancer are driven by upregulated Bcl-2 such as in lymphoid malignancies like diffuse large B cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL) [338], breast cancer [339], prostate cancer [340], small cell lung cancer [341], etc. One of the first Bcl-2 antagonists to be approved for clinical application in CLL patients was the BH3-mimetic venetoclax (ABT-199), now commercialized as navitoclax [338]. These molecules target the hydrophobic cleft of Bcl-2, thereby impeding Bcl-2's ability to counteract mitochondrial outer membrane permeabilization by pro-apoptotic Bax/Bak [342,343].

Finally, other proteins have been found to alter IP_3R levels. The ER-targeted chaperone S1R is activated upon ER Ca^{2+} depletion, resulting in its dissociation from another chaperone BiP/GRP78 and consequent binding to and stabilization of IP_3R3 [11]. Murine xenograft models of breast, lung and prostate cancer cells treated with a S1R inhibitor showed reduced tumor growth [344].

7. Conclusions and perspectives

MAMs play a crucial role in cell physiology by supporting critical mitochondrial functions and thereby ensuring adequate cell function. During the past decade, it has become increasingly clear that MAMs contain a rich network of proteins whose dysregulation or mutations are directly linked to diseases (Fig. 7). Particularly, IP_3R-GRP75-VDAC complex together with S1Rs serve as protein platforms, which directly participate in local Ca^{2+}-signaling nanodomains at the ER-mitochondrial interface. Dysregulation of IP_3R-GRP75-VDAC complex and S1Rs, being altered functional properties or altered protein levels, and/or changes in their protein-complex composition, profoundly impacts local Ca^{2+}-signaling nanodomains at the MAMs and mitochondrial physiology. The resulting aberrant Ca^{2+} signaling nanodomains at the ER-mitochondrial interface have been implicated in a broad spectrum of pathophysiological conditions and pathogenic processes – in this case clearly for WS, fPD, fALS, ATAD3A, and cancer as depicted in Fig. 7 with multiple colouring (at least three colours) of the IP_3R, GRP75, VDAC and S1R proteins. Therefore, this ER-mitochondria communication hub represents one of the promising integrative therapeutic avenues for all of the disorders reviewed in this work.

In addition to Ca^{2+}-signaling hotspots, other MAM-resident proteins, of which many are directly implicated in WS, fPD, fALS, ATAD3A and cancer, fulfill critical roles in mitochondrial quality control – PINK1, Parkin, Drp1 – or operate as ER-mitochondrial tethering mechanisms: Mfn1/2, Miro1/2. As highlighted in Fig. 7 through the multicolour (almost all of them in four colour strips) presence, the mitochondrial quality control as well as the ER-mitochondria tethering proteins may appear as another common target hub for effective therapeutic strategies. Intriguingly, these proteins, including PINK1, Parkin, Mfn1/2 are

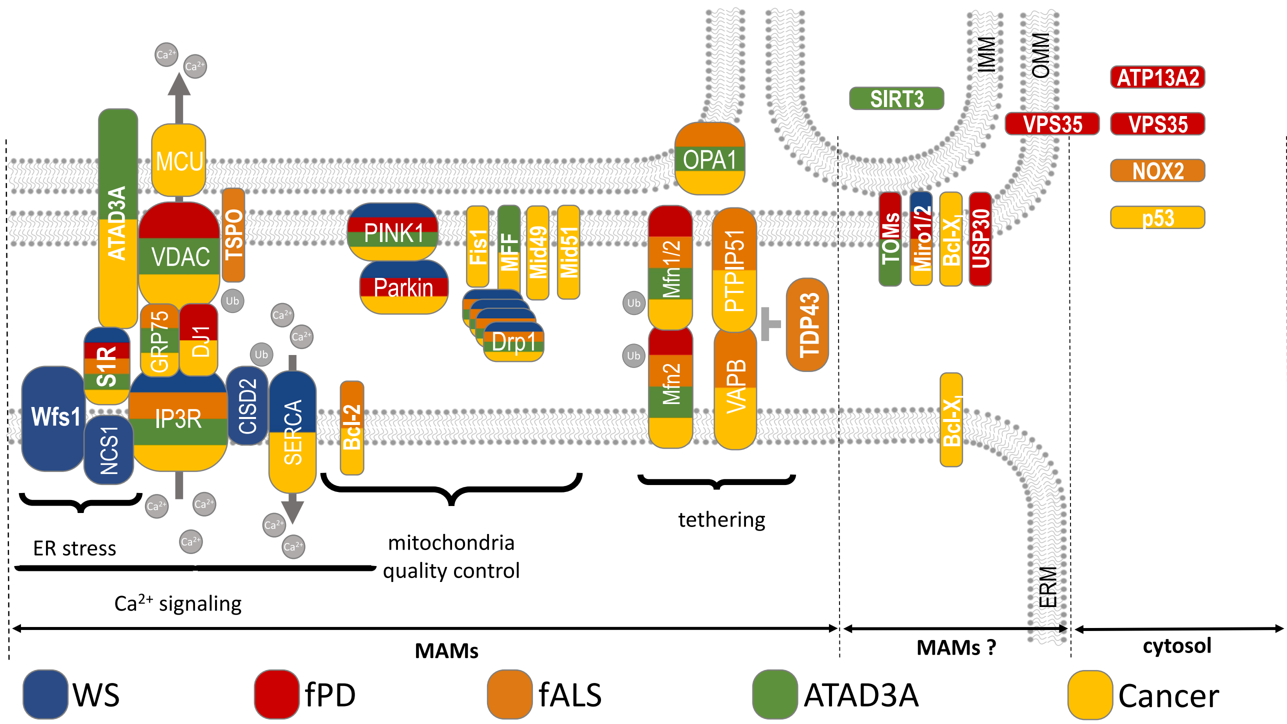

Fig. 7. Illustration demonstrating involvement of MAM proteins in Wolfram syndrome (blue), familial Parkinson's disease (red), Amyotropic Lateral Sclerosis (orange), ATAD3A related pathologies (green) and cancer (yellow). The IP_3R-GRP75-VDAC complex is beyond its main Ca^{2+} signaling function involved in ER-mitochondria tethering as well. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

well recognized for longer time already. However, the implementation of them as possible drug targets is at the moment poorly developed. This is even underscored by the fact, that these proteins significantly impact mitochondrial function and at the same time they are facing cytoplasm, thus their interaction with putative new ligands may occur more easily as direct targeting MAM luminal ER proteins or proteins located in the IMM/mitochondrial matrix.

Deepening the idea of multiple therapeutic targets at MAMs, it is important to notice at this point, that the vast majority of the MAM proteins shares multiple functions at MAMs (Fig. 7). For instance, IP_3Rs not only serve as Ca^{2+}-flux entities at the MAMs, but also operate as ER-mitochondrial tethers independently of their Ca^{2+}-transfer properties. Also, Bcl-2 proteins not only directly act at the mitochondria by preventing mitochondrial outer membrane permeabilization, but also indirectly promote mitochondrial function by acting at the level of the ER. Here, Bcl-2 proteins function as inhibitors of IP_3Rs, thereby preventing mitochondrial Ca^{2+} overload. Another example in this context are the WFS1/CISD2 proteins with their complex role for Ca^{2+} signaling both through the IP_3R-GRP75-VDAC calcium flux and through SERCA interaction, together with significant impact on ER stress and their involvement in mitochondrial dynamics. Finally, as clearly visible from Fig. 7, the multipurpose function of ATAD3A for MAM functioning has to be highlighted here, as ATAD3A shares its function in all the processes pointed out in this review: Ca^{2+} signaling, ER stress, mitochondria quality control and ER-mitochondria tethering.

On the other side, the synthesis of the data in Fig. 7 reveals the 'white spots' in the MAM-related diseases functioning network. Here, the future research direction should be focused on understanding the function of proteins, which lack multicolour labeling in Fig. 7. From these, we would like to point out special attention to WFS1/CISD2, NCS1, TSPO, TDP43 and Drp1 adaptors Fis1/Mid49/5Mid51. At the moment, the function of these proteins is known solely in one of the five disorders discussed in this review. In addition, the function of Bcl-2 and $Bcl\text{-}X_L$, two proteins well studied in the cancer field, is barely understood in the case of rare diseases until now. As all these proteins are vital MAM components, evaluating their roles in complementary diseases is of critical importance for the future research and development of effective therapeutic strategies.

As such, several diseases either during pathogenesis or at end stages are hallmarked by disrupted MAM integrity, e.g. increasing the distance between ER and mitochondria, and/or dysfunctional MAM-localized processes essential for mitochondrial health. Therefore, advancing research to develop therapeutic strategies that can improve MAM structure and/or function is a priority. Such strategies may involve direct modulation of local Ca^{2+}-transport systems together with ER stress pathways to achieve optimal results. A prototypical example of this approach is targeting the S1R, where the PRE-084 molecule has been effective in restoring the deficits in cellular and animal models of PD [148], ALS [191], and for WS [71]. Targeting S1R through new selective agonists or positive modulators or through repurposing of S1R drugs in clinical trial such as pridopidine or through S1R acting non-selective clinical drugs such as fluvoxamine [345] may thus represent therapeutic opportunities for other rare NDs and cancer treatment as well. ALS related protein TSPO could be next target for complex therapies of MAM related disorders either through its interaction with VDAC or regulation of mitophagy, as TSPO ligands Ro5–4864, PK11195, DPA-713 and DPA-714 are neuroprotective and potentially applicable for other therapeutic purposes [189]. In addition, ALS treatment compound olesoxime, targeting mPTP and interacting with TSPO and VDAC [199], may be effective for other NDs and cancer treatment through indirect correction of ER stress and Ca^{2+} signaling. Third potential therapeutic approach this review focuses on is to harmonize the ER-mitochondria tethering and thus restoring MAM integrity. This can be achieved by using molecular rulers to set the ER-mitochondrial distance for optimal Ca^{2+} exchanges between ER and mitochondria. In addition, mdivi-1, a pharmacological inhibitor of Drp1 [317]; MYLS22, an OPA1 inhibitor used in cancer research [289] or chemical compound Miro1-Reducer in case of PD [346] may be another drug repurposing focus for treatment of multiple rare diseases and cancer via balancing the optimal distance between the ER and OMM. Fourth, keeping the mitochondrial population in energetic positive condition through mitochondrial quality control represents additional important aspect, from the MAM perspective, facilitated mainly through PINK1/Parkin regulated mitophagy. Here, PD research represents so far the main contributor on this focus: carnosic acid [127], salidroside [128], KTP [133], niclosamide [135], T0466 and T0467 [129] stimulate PINK1/Parkin mediated mitophagy and provide neuroprotection. In addition, compound BIO-2007818 directly activates auto-inhibited Parkin, however, in this case without enhancing Parkin translocation rate to mitochondria and increase of mitophagy [131]. Therefore, to implement these molecules and/or to develop new molecules exploiting mitochondria quality control for NDs and cancer treatment may represent additional relevant perspective. Finally, for tackling WS, fPD, fALS, ATAD3A as well as cancer effectively, in the future one has most probably target more than one of these MAM driven pathways. This can be achieved either by multi-drug combination therapies, or through a more challenging approach, to search for a specific ligand simultaneously modulating several MAM proteins involved in Ca^{2+} signaling, ER stress, mitochondria quality control and ER-mitochondria tethering.

A final consideration relates to understand why disease-specific outcomes arise despite the fact that these pathologies share common defects in MAMs and signaling pathways. Obviously, the proteins affected in these diseases are mainly present or highly abundant in only a subset of cell types and thus will primarily impact the function of those cell types with high abundances of those proteins. As such, increased ER-mitochondrial Ca^{2+} transfers owing to the deregulation of a specific protein and its associated protein network can result in neurodegenerative outcomes (for proteins critical for neuronal function) but equally well prevent oncogenesis (for proteins functioning as tumor suppressors). Another factor related to the tissue and cellular specificity is the differentiation state of cells. In the case of neurodegeneration, the neurons are terminally differentiated high level integrity cells. On the contrary, cancer cells represent the other extreme with uncontrolled division rate and plethora of compensatory mechanisms to maintain just basal survival condition. Another aspect may be the metabolic activity. Although both, neurons and cancer cells have to fulfill high energetic requirements, their metabolic resources, substate metabolism and energy production effectiveness differ significantly. As such, a reduction in ER-mitochondrial Ca^{2+} transfers may result in a metabolic crisis in neurons, thereby hampering their survival while it could yield a cell survival advantage in cancer cells rendering them resistant to ongoing oncogenic stress. Moreover, the level of impairment of ER-mitochondrial Ca^{2+}-transfer could dictate the outcome. Indeed, while reduced ER-mitochondrial Ca^{2+} transfer can enable cells to cope with ongoing oncogenic stress or to render them resistant to chemotherapeutics, a complete whipe-out of ER-mitochondrial Ca^{2+} transfer could induce cancer cell death due to mitotic catastrophe. In such events, uncontrolled cancer cell proliferation requires sufficient mitochondrial Ca^{2+} to drive mitochondrial bio-energetics and sustained production of mitochondrial substrates for nucleotide biosynthesis [243]. Normal cells can withstand such profound blocks of ER-mitochondrial Ca^{2+} transfers with subsequent mitochondrial bio-energetic crisis by tuning down their proliferation and activating processes such as autophagy. Cell micro-environment and supporting tissue specifics are the next point why molecular disruptions in MAMs may lead to distinct pathological features. Final mark is the time lapse of the specific pathology. In case of neurodegeneration, the process of cell loss may reach decades, whereas cancer cells prograde rapidly. Although MAMs are substantial part of the pathology, the additionally activated molecular signaling pathways may largely differ.

All in all, it will be of crucial importance to translate bench approaches into clinically relevant strategies. Here, the repurposing of existing, FDA-approved drugs and/or focusing on targets for which already pharmacological tools have been developed and used in the clinic such as S1R controlling ER-mitochondria Ca^{2+} flux and ER stress, PINK1/Parkin mediated mitochondria quality control, Mfn1/2/VAPB-PTPIP51/Miro1/2 facilitating ER-mitochondria tethering are important avenues that should be explored in the coming years.

CRediT authorship contribution statement

Michal Cagalinec: Writing – review & editing, Writing – original draft, Conceptualization. **Adnan Mohd:** Writing – review & editing, Writing – original draft. **Silvia Borecka:** Writing – review & editing, Writing – original draft. **Geert Bultynck:** Writing – review & editing, Writing – original draft, Conceptualization. **Vinay Choubey:** Writing – review & editing, Writing – original draft. **Shira Yanovsky-Dagan:** Writing – review & editing, Writing – original draft. **Shlomit Ezer:** Writing – review & editing, Writing – original draft. **Daniela Gasperikova:** Writing – review & editing, Writing – original draft. **Tamar Harel:** Writing – review & editing, Writing – original draft. **Dana Jurkovicova:** Writing – review & editing, Writing – original draft. **Allen Kaasik:** Writing – review & editing. **Jean-Charles Liévens:** Writing – review & editing, Writing – original draft. **Tangui Maurice:** Writing – review & editing, Writing – original draft, Conceptualization. **Marco Peviani:** Writing – review & editing, Writing – original draft. **Elodie Marie Richard:** Writing – review & editing. **Jan Skoda:** Writing – review & editing, Writing – original draft. **Martina Skopkova:** Writing – review & editing. **Pauline Tarot:** Writing – review & editing. **Robbe Van Gorp:** Writing – review & editing, Writing – original draft. **Liga Zvejniece:** Writing – review & editing. **Benjamin Delprat:** Writing – review & editing, Writing – original draft, Conceptualization.

Consent for publication

All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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