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REVIEW ARTICLE

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Endoplasmic reticulum stress: A possible connection between intestinal inflammation and neurodegenerative disorders

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Abstract

Background: Different studies have shown the key role of endoplasmic reticulum (ER) stress in autoimmune and chronic inflammatory disorders, as well as in neurodegenerative diseases. ER stress leads to the formation of misfolded proteins which affect the secretion of different cell types that are crucial for the intestinal homeostasis.

Purpose: In this review, we discuss the role of ER stress and its involvement in the development of inflammatory bowel diseases, chronic conditions that can cause severe damage of the gastrointestinal tract, focusing on the alteration of Paneth cells and goblet cells (the principal secretory phenotypes of the intestinal epithelial cells). ER stress is also discussed in the context of neurodegenerative diseases, in which protein misfolding represents the signature mechanism. ER stress in the bowel and consequent accumulation of misfolded proteins might represent a bridge between bowel inflammation and neurodegeneration along the gut-to-brain axis, affecting intestinal epithelial homeostasis and the equilibrium of the commensal microbiota. Targeting intestinal ER stress could foster future studies for designing new biomarkers and new therapeutic approaches for neurodegenerative disorders.

KEYWORDS
ER stress, gut-brain axis, intestinal inflammation, neurodegenerrative diseases

1 | INTRODUCTION

The ER represents one of the largest and most complex organelles in the eukaryotic cell. It is formed by tubules and sacs (*cisternae*) interconnected in a network that extends from the nuclear membrane to the cytoplasm.[1] The major function of the ER, together with the Golgi, is to drive the synthesis, the folding and the correct maturation of proteins. Indeed, in the ER proteins acquire their three-dimensional conformation and undergo posttranslational modifications, through the activity of chaperones resident in the ER lumen that guide the correct folding process.[2,3] Only 20% of newly synthesized proteins achieve complete maturation and are released by the ER, due to a rigorous quality control. The latter is under the regulation of the ER-associated protein degradation system (ERAD), which consists in the degradation of misfolded proteins by the proteasome associated to the ER membranes.[4] Failure in ERAD control leads to the

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accumulation of misfolded proteins that promotes the activation of the *unfolded protein response* (UPR), which aims to restore ER homeostasis. In addition to the excessive protein misfolding, the correct functioning and processing of the ER can be perturbed by different factors, such as: altered lipid composition or lipid peroxidation, iron imbalance, Ca^{2+} leakage, viral infections, and hypoxia. All of these factors can disrupt ER homeostasis leading to ER stress[5] (Figure 1).

Different pathways involved in ER stress have been described with an increasing degree of complexity and heterogeneity during evolution. These pathways are under the control of three ER resident transmembrane proteins: inositol requiring enzyme-1 [IRE1], protein kinase RNA-like ER kinase [PERK], and activating transcription factor 6 [ATF6]. Particularly, IRE1 is the evolutionary oldest sensor of the ER stress. Invertebrates have all the three ER-proteins (IRE1, PERK, and ATF6), whereas vertebrates showed two homologues of IRE1 (IRE1α and IRE1β) and ATF6 (ATF6α and ATF6β) and one PERK. The molecular paralogs are responsible for an intertwined regulation of IRE1 and ATF6 pathways[6,7] (Figure 2).

Increasing evidence supports the central pathogenetic role of ER stress in different diseases, such as neurodegenerative disorders, diabetes, obesity, and chronic inflammatory bowel diseases (IBD).[8,9] In all these pathological conditions activation of ER stress occurs and an inflammatory response, subsequent to ER stress, represents a common and invariable pathogenetic actor. Conversely, the role of ER stress as primary and causative actor of disease is controversial.[10,11] Although ER stress is invariably present in both Parkinson's disease (PD) and Alzheimer's disease (AD), in these pathologies, it represents the consequence of protein misfolding and neuroinflammation.[12] Only in amyotrophic lateral sclerosis (ALS) genetic mutations of proteins involved UPR and ER stress response, have been directly linked to the development of neurodegeneration. PERK haploinsufficency has been linked with worsening of motor-neurons degeneration in SOD1 mutant mice,[13] while mutations and polymorphisms of the ER chaperone protein disulfide isomerase (PDI) have been identified in ALS patients[14] and associated with disrupted connectivity of spinal motor-neurons.[15] Moreover, mutations in genes encoding for ER proteins have been directly linked with familiar forms of ALS, such as the mutation of Sigma 1 Receptor (SIGR1), involved in ER proteins homeostasis and regulation of RNA-protein binding.[16]

The key role of the gut-to-brain axis in the development of neurodegenerative disorders is progressively consolidating overtime. In accordance, it has been reported in different cohorts that patients affected by IBD present an increased risk of developing neurodegenerative disorders.[17,18] Furthermore, alterations in gut microbiota and its molecular products, defined as gut dysbiosis, are responsible for facilitating a wide range of pathologies, including neurological and psychiatric disorders,[19–21] also via the activation of ER stress.[22,23] Tryptophan-derived metabolites, short chain fatty acids, and LPS, that comes from bacteria, can cross the intestinal barrier, enter the circulation, cross the blood–brain barrier and, reaching the brain, play a key role in the microbiota-gut-brain cross-talk.[24,25]

Indeed, several studies have investigated the role of gut microbiota in different neurological disorders and particularly in PD and synucleinopathies.[26–28] The correlation between the host immune system (chemokines, TNF-α, IL-6, and IL-17) and different species of gut microbiota, have been widely reported. Specifically, there is a negative correlation between beneficial bacteria (*Lactobacillus* and *Bifidobacterium*) and host immune system; contrary, there is a positive correlation between opportunistic pathogenic bacteria (*Escherichia* and *Shigella*) and host immune system. This interaction is responsible of triggering inflammation during dysbiosis and in course of both IBD and neurodegenerative disorders.[29–31] Dysbiosis frequently occurs in PD and enhances inflammatory response, leading to α-syn misfolding and phosphorylation, by activation of MyD88-dependent toll-like receptors (TLRs) in neuronal and glial cells,[32,33] as well as in enteric neurons,[34] thus bridging neurodegeneration with intestinal inflammation.[25]

All the mechanism above, highlight how neuronal and humoral connections between the nervous system and the digestive tract contribute to neurodegeneration by the spreading of misfolded proteins and triggering neuroinflammation.

Hence, in the present review, we aim to explore ER stress pathways in chronic IBD and neurodegenerative disorders, by providing a comprehensive overview of possible common pathogenetic mechanisms between these challenging and intertwined pathologies.

Key points

- The gut-brain axis and the endoplasmic reticulum stress role in inflammatory bowel disease and in neurodegenerative disease are not yet well-understood.
- This review makes the state-of art of the current knowledge on cross talk between gut and brain, focusing on ER stress induction and protein misfolding during inflammatory and neurodegenerative diseases.
- The deep knowledge of these pathological mechanisms is required to be able to study new diagnostic and therapeutic approaches applicable to neurodegenerative and inflammatory diseases.

2 | ER STRESS IN IBD

2.1 | The intestinal barrier

The intestinal epithelium, the front line of normal body defense, provides a barrier that selectively and actively absorbs nutrients and water, but protects the host from the invasion of foreign antigens, microorganisms, and their toxins.[35]

To protect the intestinal mucosa from detrimental invasion of microorganisms, the intestinal epithelial cells produce a physical and chemical barrier. The first type of barrier includes: (i) the mucus layer, which coats the intestinal mucosa, (ii) the glycocalyx on the microvilli of absorptive intestinal epithelial cells, and (iii) the

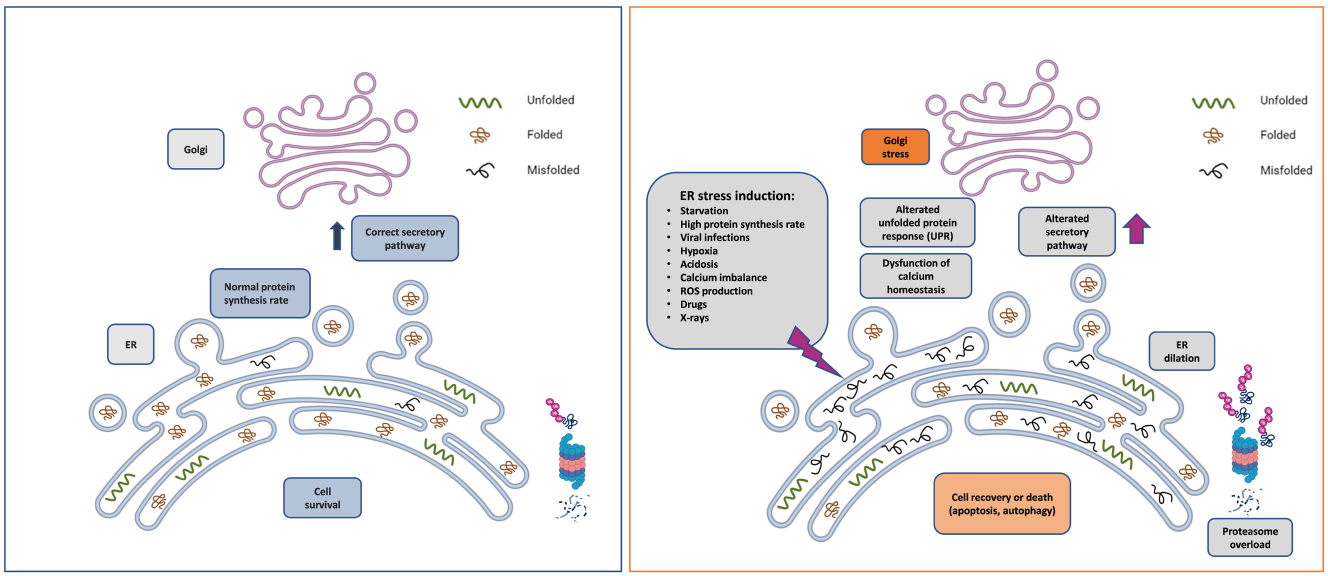

FIGURE 1 ER in healthy and chronic conditions. On the left, the panel illustrates the structure of the ER in healthy conditions, showing the physiological mechanism of protein trafficking. The right panel shows ER in condition of chronic stress and protein misfolding. Particularly, persistent ER stress promotes the activation of unfolded UPR signaling to maintain cell viability and function, restoring ER homeostasis. However, persistent ER stress leads to altered calcium homeostasis, Golgi stress, and alteration of cell vesicles trafficking.

intracellular junctions (tight junctions, adherens junctions, and desmosomes) that firmly stabilize the mechanical cohesion of intestinal epithelial cells.[36]

Claudin and occludin, transmembrane proteins, are the most important constituent of the tight junctions which forms a solid seal between the cells and representing a fundamental component of intestinal barrier. Recent studies of IBD development suggest that inflammation increases gut leakiness in part through alterations of claudin expression and localization[37] and that this leakiness promotes the probability that gut antigens will invade the submucosa, further exacerbate inflammation and pathology.[38]

The chemical barriers is formed by various antimicrobial peptides (AMPs) and the Reg3 family proteins, which are regulated by intestinal environmental factors and immune cell-derived cytokines. These barriers act in a concerted and cooperative manner and efficiently represent a spatial segregation to prevent unnecessary conflict between the microbiota and host immune cells, maintaining their symbiotic relationship in the intestine.[36]

A second layer of protection to the invasion of microbes toward the intestinal mucosa is represented by the gut vascular barrier (GVB), lying in close proximity of the epithelial barrier. In physiological conditions the GVB is selectively permeable and blocks microbial dissemination into the portal and the systemic circulation.[39]

Destruction of the intestinal barrier determines the development of different gastrointestinal and systemic disorders, including IBD.[40]

Indeed, in healthy conditions, the efficient multilayered defense barrier is able to protect the intestinal mucosa against insults from the intestinal lumen, whereas in IBD patients the intestinal barrier could be compromised at different levels. Some examples are the following: modifications of the mucus layer, a defective AMP production, unresolved ER stress, alterations in the process of autophagy as well as an increased epithelial permeability leading to increase the vulnerability of the epithelium to bacterial invasion. Consequently, the protective host-defense mechanisms finally result in chronic intestinal inflammation.[41] In accordance, the intestinal barrier may be affected by changes in the diversity, composition, and resilience of the intestinal flora producing an imbalance of microbial communities.[42] At last, the gut immune barrier represents one of the most dynamic and complex features to be elucidated. The intestinal lumen can be considered in direct contact with the outside and it requires an articulated defense system. To protect itself from possible pathogenic external factors, such as pathogenic microorganisms, the intestine promotes an inflammatory response and releases several toxins and chemical compounds. Gram-negative bacteria are a source of lipopolysaccharides (LPS) and the interaction of LPS with the toll-like receptor 4 (TLR4), expressed by macrophages, induce the production of inflammatory cytokines.[43]

Furthermore, recent evidence has revealed that both damaged intestinal epithelial integrity and intestinal barrier dysfunction are crucial to increase intestinal permeability.[44]

2.2 | The cells of the intestinal epithelial barrier (IEB)

IEB consists of a continuous monolayer of proliferating intestinal epithelial cells. The intestinal stem cells (ISCs) are located at the base of the crypts and produce five different cell types: enterocytes, the goblet cells (GCs), the tuft cells, the enteroendocrine cells (EECs), and the Paneth cells (PCs).[45] In particular, in 1888, the Austrian physiologist and histologist Joseph Paneth observed the presence of pyramidal-epithelial cells at the base of the small intestinal crypts that were

rich of secretory granules and were called PCs.[46,47] Histochemical analysis has shown elevated expression of zinc and enzymes in the cytoplasm of human PCs, which suggest the contribution of these cells in the digestive processes.[48] Nowadays, the function of PCs is strictly related to the intestinal homeostasis. These cells can release different molecules, including antimicrobials, to control and modulate gut microbial communities.[49] Accordantly, the PCs respond to changes in microbial composition by secreting different factors, which form a protective biochemical barrier from adhesion, hyperproliferation and translocation of the intestinal microbial population.[50] Studies have reported that (i) the PCs number increased with the bacterial insemination's growth in the small intestine, and (ii) PCs are found throughout the colon in inflammatory condition, where they are usually absent.[51] The PCs' granules are formed by various antibacterial proteins: lysozyme, α-defensins (HD5 and HD6), secretory phospholipase A2 (sPLA2), and angiogenin-4 (Ang4). These compounds are secreted into the intestinal lumen in response to various stimuli.[52] Therefore, a balance between the bacterial species colonizing the intestinal mucosal surface and the PCs leads to maintain a beneficial bacterial composition and homeostasis.[53] Alteration of PCs functions has been associated with several human intestinal diseases, including IBD.[54] PCs are involved in acquired immunity at the level of intestinal mucosa,[55,56] representing a leukocyte-like cell involved in intestinal immunity.[57,58] Being highly secretory cells, PCs are characterized by a widely active ER, involved in secretion and folding of proteins and enzymes. Consequently, they are particularly sensitive to ER stress.[59] Elevated ER stress induces dysfunction in PCs secretion or secretion of misfolded α-defensin (antimicrobial peptide) with less effective antimicrobial properties.[60,61] Moreover, Grootjans et al.[62] demonstrated that ischemia/reperfusion injury of the ileum can induce ER stress in PCs with increased activation of the UPR and increased splicing of the XBP1. Prolonged activation of the UPR can finally sort in apoptosis of the PCs through the activation of C/EBP homologous protein (CHOP) transcription factor, which promotes the activation of caspase-3. The derived lack of PCs leads the development of dysbiosis and the increasing levels of inflammatory cytokines in the bowel and in the systemic blood.[58,63] Therefore, the PCs can be considered as a main target for ER stress signaling and they have an important role in maintaining intestinal homeostasis toward three main mechanisms: (i) regulation of the microbiota, (ii) maintenance of the gut stem cell niche, and (iii) modulation of the inflammatory response during intestinal injuries.[64]

Another crucial type of epithelial cell is represented by the goblet cell (GC), firstly identified in 1837 by the German physician Jakob Henle in the mucosa of the small intestine. In 1866, GCs derived their name from their typical shape, which resembles the shape of a cup (drinking goblet), due to the presence of the mucous droplets at the apical domain.[65–67] Gut GCs originate from a common progenitor cell (intestinal stem cell), which also differentiates into enterocytes, PCs, and tuft cells.[68,69] The biosynthesis of mucus and its major components (mucin-2, Fcγ binding protein, and calcium-activated chloride channel regulator1 (CLCA1)) are finely regulated by both control mechanisms on the ER and protein chaperones that assist the assembly and subsequent maturation of proteins in the Golgi apparatus.[70] During its biosynthesis, mucin-2 begins the maturation at the level of the ER, where proper folding, carboxy-terminal disulfide-mediated dimerization and initial N-glycosylation take place. Subsequently, in Golgi, mucin-2 is O-glycosylated by glycosyl transferases and transformed into densely packed multimers within secretory vesicles at low pH and high calcium concentration environment.[71,72] Certain goblet cell-specific proteins, such as chaperone protein AGR2 (anterior gradient 2) and stress-sensor protein IRE1β, induce altered mucus production, and facilitate the intestinal inflammatory process when they are dysregulated.[73] *Agr2*$^{-/-}$ mice show significant reduction of GCs, abnormal expansion of PCs with increased ER stress and occurrence of colitis and ileitis.[74] As previously mentioned, IRE1β represents a sensor of ER stress. In IRE1$\beta^{-/-}$ mice, mucin-2, accumulated in ER of GC, increases the splicing of XBP1, thus further amplifying ER stress and inducing ER distention. IRE1 and PERK detect the correct protein folding in the ER by the association of luminal domains with chaperone BiP. In this binding form, BiP maintains the monomeric state of IRE1 and PERK transmembrane proteins. In ER stress conditions, BiP is dissociated and IRE1 and PERK are oligomerized[75,76] (Figure 2). BiP can bind directly to the unfolded proteins, actively fold its substrates (foldase activity) and it also acts as an ER stress sensor.[77] GCs require a finely regulated mechanism of ER stress control, and an increase in mucus turnover induces an additional pressure on protein synthesis machinery. If the number of misfolded proteins is very high, the GC undergoes apoptosis. Depleted GCs and a reduced mucus layer is observed during inflammation and ulcerative colitis (UC).[78] In agreement, several studies suggested that goblet ER stress may contribute to the pathogenesis of Crohn's disease (CD) and UC by inducing epithelial cell apoptosis and consequent reduction of physiological mucus secretion in the gut[22,79,80] (Figure 2).

A third important cell type in the gut homeostasis is represented by the EECs. These heterogeneous cell population is distributed along the entire gastrointestinal mucosa (representing 1% of the gut cell population), mainly at the level of intestinal crypts. Physiologically EECs are hormone- and neuropetide-secreting cells, including a population of cells known as APUD (amine-precursors uptake and decarboxylation) cells, due to their ability in decarboxylating 5-hidroxytriptofane into 5-hydroxitriptamine (serotonin).[81] Accumulating evidences suggest that EECs are important sensors of the gut microbiota and microbial metabolites, secreting hormones in response to the microbial factors and providing a bridge between inflammatory/immune response and afferent neuronal fibers.[82] Hormones and neuropeptides produced by the EECs have a variable effect on intestinal inflammation. In particular: serotonin, neuropeptide Y (NPY), and substance P (SP) are typically pro-inflammatory, whereas chromogranin/secretogranin family peptides, vasoactive intestinal peptide (VIP), ghrelin, and somatostatin disclose anti-inflammatory activity.[83] EECs are affected in course of IBD and recent studies have shown that IBD patients typically have altered production of the pro-hormone chromogranin (CHG)-A, which is a strong driver of inflammation and correlates with disease

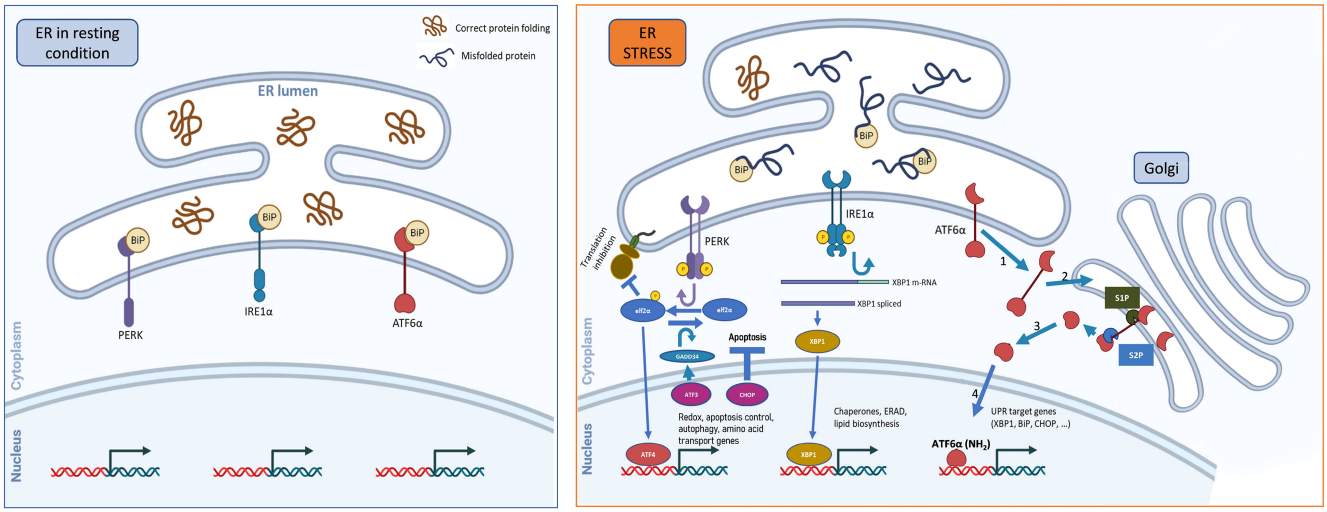

FIGURE 2 Left panel shows a schematic representation of the activity of the ER in physiological conditions. The right panel shows a schematic representation of ER under stress conditions within the cell. ER stress-mediated accumulation of misfolded proteins promotes the activation of the PERK, IRE1α, and ATF6 stress sensor through the molecular chaperone Bip.

activity.[84,85] Moreover, certain EECs directly secrete IL17, which has been also related to progression and activity of CD,[86] while G-WAS and genetic studies closely associate alteration of EECs with the development and the severity of CD.[87,88] Being highly secreting cells, also EECs are very sensitive to ER stress, as is proved by the crucial contribution of ER stress in the dysfunction of pancreatic endocrine cells during Type II diabetes.[89–91] Among them, L-cells, producing glucagone-like peptide 1 (GLP-1) are the most sensitive to ER stress and UPR, since they are prone to gluco- and lipotoxicity.[92] Interestingly, GLP-1 is increased in patients with CD, with consequent increased inflammatory response, altered intestinal barrier, and reduced appetite.[93–95]

2.3 | IBD and the role of ER stress

IBD can be identified as a nonspecific chronic mucosal disease and its pathogenesis depends on a complex association between genetic, environmental, and immunological factors.[96] The two major forms of IBD are UC and CD. The first one is limited to the colon and characterized by a continuous mucosal inflammation which starts in the distal part and can extend proximally along the entire colon; whereas, the second can affect any region of the gastrointestinal tract, especially the terminal ileum, with chronic discontinuous inflammation and ulceration.[97]

Several studies suggest that ER stress is involved in the pathogenesis of IBD. In fact, it has been demonstrated that there is an interplay between intestinal inflammation and ER stress, with the dysregulation of the intestinal epithelial homeostasis. As previously mentioned, intestinal epithelium is exposed to: (i) an enormous range of factors derived from both host and microbial metabolism, and (ii) signals from the complex immune compartment that is in relation with the epithelium.[98] Perturbations in the function of intestinal epithelial cells promote microbial dysbiosis and hyperactivation of immune cells in the lamina propria, which determine the IBD development.[99]

For instance, the transcription factor XBP1 (X-Box Binding Protein 1) interact with JNK (c-Jun N-terminal kinases) activation in the development and maintenance of secretory cells. Disruption of XBP1 promotes ER stress in intestinal epithelium, which results in spontaneous enteritis. This occurs because of the inability of XBP1-deficient IECs to properly generate antimicrobial activity and respond appropriately to inflammatory signals. It has been demonstrated that hypomorphic variants in *XBP1* gene locus increase the possibility to develop IBD. Hence, this makes the ER stress pathway a common genetic contributor to IBD in the human population.[60] Moreover, studies observed that inflammatory mediators and metabolic changes in the intestinal environment promote ER stress responses, as revealed by the action of IL-10 on the TNF-induced ER stress. Proteomic analysis in *E. faecalis*-mono associated *IL-10*$^{-/-}$ mice demonstrated that the expression of the ER stress response protein grp-78 was elevated in IECs under conditions of chronic inflammation; as well as IL-10 was able to inhibit the inflammation-induced ER stress response by modulating ATF-6 nuclear recruitment to the grp78 gene promoter.[100] This intestinal chronic inflammation can be associated with an abnormal pattern of mitochondrial DNA (mtDNA) deletions, which may occur during repair of damaged mtDNA.[101] It can therefore be assumed that inflammatory mediators and metabolic changes in the intestinal environment contribute to ER stress responses, which in turn exacerbate the bowel inflammation.[102] In fact, the deregulation of both ER stress and UPR signaling pathways can induce or amplify the inflammatory response in IBD.[103] Finally, other studies revealed a possible link between ER stress, production of misfolded proteins and genesis of abnormal epitopes by proteasome degradation, that together can induce an immune response against intestinal cells.[104,105] Taken together, these results support the hypothesis that ER stress exerts its multifaceted role on IBD, through a complex and intertwined interaction with inflammatory, immunity and metabolic pathways.

3 | ER STRESS IN NEURODEGENERATIVE DISEASES

3.1 | Synucleinopathies

PD, together with multiple system atrophy (MSA), pure autonomic failure and dementia with Lewy bodies (DLB) belongs to a group of neurodegenerative disorders in which intraneuronal and intra-glial aggregation of the pre-synaptic protein α-synuclein (α-syn) represents the pathological hallmark. Mechanisms responsible of α-syn aggregation are diverse among the different synucleinopathies and depend on the biology of the different cell types specifically involved. Among different cell types, dopaminergic (DA) neurons and spinal motor neurons result particularly sensitive to the development of ER stress and to the occurrence of α-syn misfolding and aggregation, as reported in toxic and transgenic animal models of parkinsonism.[106–108]

Indeed, UPR activation markers, including phosphorylation of PERK, eIF2α, and IRE1α, have been observed postmortem in neuromelanin-containing DA neurons of PD patients,[109,110] where they were co-localized with intracellular α-syn aggregates[109] (Figure 3).

Moreover, ER stress represents an invariable pathogenetic pathway in toxic models of parkinsonism based on oxidative stress and mitochondrial dysfunction, such as those obtained by treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, and 6-hydroxydopamine (6-OHDA).[111–114]

α-Syn oligomers are the species responsible for both α-syn toxicity and intercellular spreading and they are strong drivers of ER stress and UPR. At the early stages of synucleinopathies, α-syn oligomers accumulate in the ER[115] and bind to both GRP78 and ATF6.[116,117] By targeting GRP78, α-syn oligomers activate PERK pathway[118]; whereas, by binding to ATF6, they inhibit the ERAD, fueling further α-syn misfolding and oligomers formation.[117] Mutated and phosphorylated forms of α-syn interfere with the proper protein folding and posttranslational modification by affecting at different levels the protein trafficking between ER and Golgi.[119,120] Several studies have reported that the overexpression and misfolding of α-syn induce traffic defects of lipids vesicles that starts at the synaptic terminals and later expands in a retrograde manner to the Golgi and the ER,[121] also inducing Golgi and ER fragmentation.[122,123] Interestingly, the toxicity of α-syn oligomers bound to lipid vesicles is dramatically higher in comparison to unbounded α-syn. These evidences support the idea that a direct interaction of α-syn with the membranes of the ER and the Golgi is a crucial event for α-syn aggregation and toxicity.[124] Moreover, because of ER calcium levels are particularly sensitive to the increase of reactive oxygen species (ROS), α-syn oligomers may also contribute to ER stress by impairing mitochondrial function and respiratory chain, interacting with outer and inner mitochondrial membranes.[125] Accumulated lipids can bind to α-syn, accelerating its aggregation into oligomers and fibrils, which are responsible of a further ER dysfunction.[126,127] In addition, lipid accumulation can be targeted for lipid peroxidation with the generation of lipids peroxides and reactive aldehydes. These can exert ER stress, together with lipotoxicity, disruption of lipids membranes, and further mitochondrial dysfunction.[128,129]

3.2 | Tauopathies and AD

Tau aggregation in filamentous intracellular inclusions is a signature marker of primary tauopathies (e.g., progressive supranuclear palsy and cortico-basal degeneration) and of AD, in which intracellular tau tangles coexist with extracellular plaques of amyloid-beta.

As the altered protein aggregates in neurodegeneration, tau misfolding and hyperphosphorylation can induce ER stress. Moreover, hyperphosphorylated tau might be also able to directly induce the phosphorylation of PERK with the downstream activation of NF-kappa B, even in the absence of the ER stress, as has been also reported for α-syn and Huntington (Hgt) aggregation.[130,131] Accordantly, in AD brains, Buchanan et al.[132] have demonstrated that tau neurofibrillary tangles (NFTs) are correlated with PERK

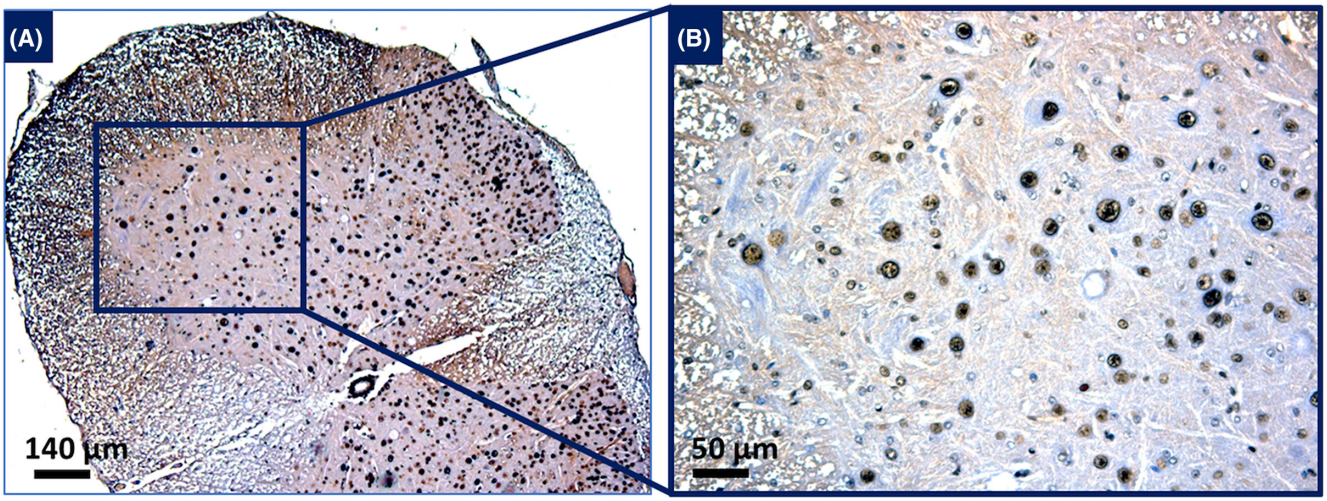

FIGURE 3 Representative immunohistochemical staining for p-PERK (typical marker of ER stress), detected in perinuclear region of spinal motor neurons, after chronic treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Original magnification 5× (A), 20× (B).

phosphorylation and neuroinflammation in the temporal cortex. Moreover, phosphorylation of PERK has been reported in the hippocampal neurons of AD patients. These data correlated to diffuse expression of hyperphosphorylated tau, even before the occurrence of NFTs, indicating that activation of the ER stress cascade might represent an early event in tau-related neurodegeneration.[133]

In vitro experiments have shown that tau accumulation within the cells is associated with the inhibition of the ERAD and the consequent accumulation of ubiquitinated proteins. Moreover, ER stress induces tau phosphorylation and tau cleavage by the caspase 3. Cleavage of phosphorylated tau might produce seeding-competent tau species, which are in turn responsible of the spreading of tau pathology throughout the nervous system.[134] The production of seeding competent tau species further bridges ER stress with neuroinflammation and proteasome dysregulation. Neurons with tau aggregates abnormally expose high amounts of phosphatidylserine because of ER stress, mitochondrial dysfunction, and consequent production of ROS. Phosphatidylserine, leads microglia to identify neurons affected by tau aggregation, promoting their phagocytosis.[135] After phagocytizing tau aggregates-bearing neurons, microglia become hypophagocitic and release seeding-competent tau aggregates, which promote tau pathology progression.[136] Microglia, in contact with tau aggregates-bearing neurons, activate NF-kappa B pathways, increasing the production of inflammatory cytokines, and promote the synthesis of nitric oxide (NO), another positive modulator of ER stress and UPR activation.[137]

Next, ER stress determines tau aggregation as well as promoting the progression of tau pathology, by targeting microglial response and proteasome dysfunction. In AD, both tau intracellular NFTs and extracellular Aβ plaques can induce ER stress, which at the initial stages is aimed at preventing progression of AD pathology. In advanced stages of AD, the severity of protein aggregation and the prolonged exposure of the ER to misfolded proteins are associated with irreversible ER stress and excessive UPR.[138] All these lead to neuroinflammation through NLRP3 inflammasome activation, thus bridging again protein misfolding, ER stress, and neuroinflammation.

3.3 | ER Stress and neuroinflammation in neurodegenerative disease

ER stress represents a key pathogenetic mechanism in neurodegenerative diseases. Protein misfolding—the signature pathological hallmark of neurodegeneration—can be either the cause or the consequence of ER stress. However, the severe accumulation of misfolded proteins and the chronic exposure to ER stress correlates with a maladaptive UPR response, where an excessive UPR activation leads to a vicious cycle ending with the development of neuroinflammation and cell death.

As reported above, three different molecular pathways correlate with the activation of UPR following ER stress: the IRE1α branch, the PERK branch, and the ATF6 branch. All of them converge in the activation of the nuclear factor kB (NF-kB) which is in turn responsible of the expression of inflammatory cytokines such Tumor necrosis factorα (TNFα), IL-1, IL-6, and IL-8[139,140] (Figure 4).

In the cytoplasm, activated IRE-1α binds to the transducer protein TRAF-2 (TNF receptor-associated factor 2) and recruit the inhibitory kB kinase (IkB) complex. The binding of TRAF-2 with IkB kinase increases IkB phosphorylation and ubiquitination. Degradation of IkB by the proteasome is responsible of NF-kB translocation into the nucleus, which promotes transcription of cytokines genes.[142,143] Activation and phosphorylation of PERK leads to inhibit protein synthesis, with specific untranslated mRNA. Among these mRNAs, there is also IkB mRNA, which results inhibited in its translation after chronic phosphorylation of PERK. Reduced synthesis of IkB represents a further mechanism leading to increase both levels of activated NF-kB and expression of inflammatory cytokines.[144,145] Finally, activation of the ATF6 branch induces the activation of cyclic AMP-responsive element-binding protein 3-like 3 (CREB3L3 and CREBH) transcription factor with the consequent activation of the protein kinase B and the downstream activation of NF-kB.[146,147]

Collectively, these studies outline that there is a link between ER stress and neuroinflammation in different neurodegenerative disorders, including synucleinopathies, tauopathies, and AD.

4 | THE ROLE OF ER STRESS ALONG THE GUT–BRAIN AXIS

The gut-to-brain axis has disclosed a pivotal role in the development of neurological disorders, highlighting how nervous and humoral connections between digestive tract and nervous system cooperate in the process of neurodegeneration, toward protein misfolding and production of pro-inflammatory cytokines. Accumulation of misfolded proteins is an invariable consequence of ER stress and interestingly, all the pathways activated by ER stress converge onto inflammatory response and drive the expression of pro-inflammatory cytokines. On the other hand, circulatory inflammatory cytokines derived from the gut can drive a pro-inflammatory phenotype in microglia, further worsening protein misfolding and neurodegeneration in the nervous system.

Prolonged exposure to misfolded proteins induces a non-adequate UPR, which leads to programmed cell death and triggers inflammatory response.[138] Neuronal cells are characterized by a limited potential of renewal, and they may undergo prolonged ER stress, which leads to a continuous and irreversible formation of protein aggregates with the biochemical features of beta-sheet fibrils (amyloid conformers). Prolonged ER stress is also related to the activation of secondary pathways, including NF-kappa B pathway, which is responsible for the link between ER stress and neuroinflammation.[148] Finally, neuroinflammation and microglia activation have been related to worsening of neurodegeneration and propagation of proteinopathy throughout the nervous system.[136]

In the gut, ER stress mainly involves cells with high secretory phenotype, including PCs and GCs, leading to dysfunctional defense barrier, altered intestinal permeability and unbalanced composition of the gut microbiota.[149] In contrast, studies suggest that

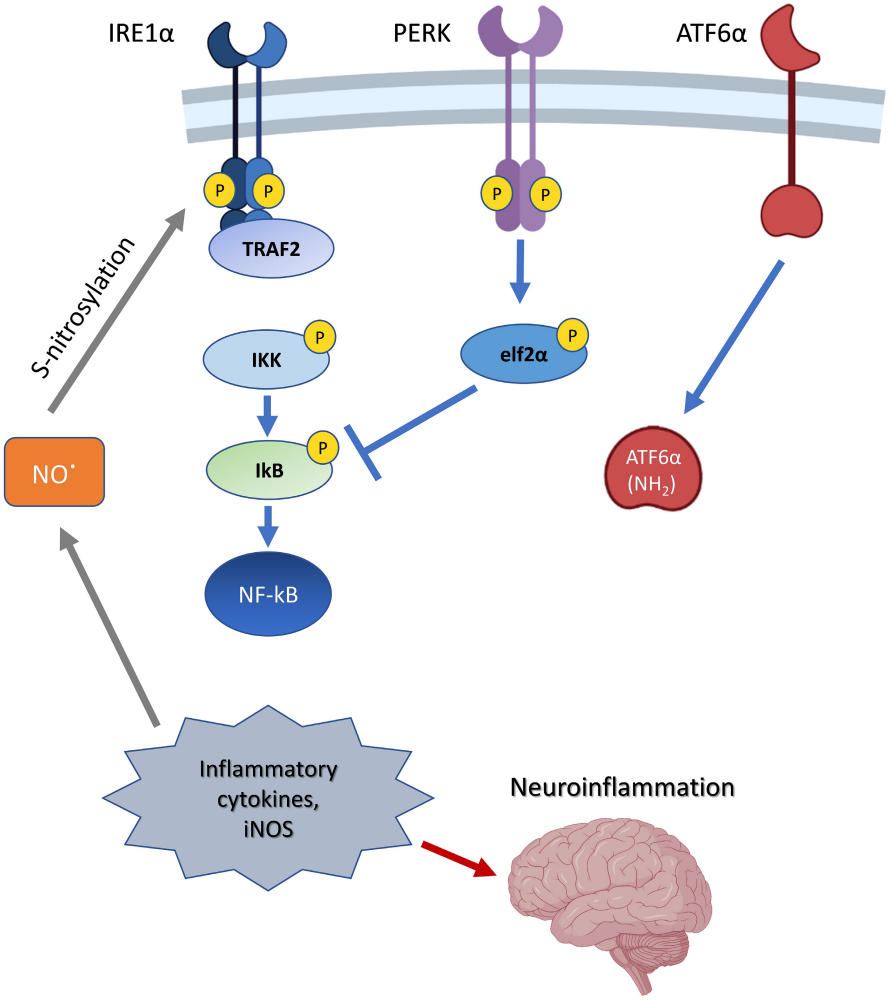

FIGURE 4 Schematic representation of three different molecular pathways that correlate with the activation of UPR following ER stress: the IRE1α branch, the PERK branch, and the ATF6 branch. All of them determine the activation of the nuclear factor kB (NF-kappa B) which is in turn responsible for inflammatory cytokines secretion. TRAF-2 also activates c-Jun and JNK pathways, contributing to the development of neuroinflammation. NO, produced during inflammation by iNOS, can inhibit IRE1a by S-nitrosylation mechanism.[141]

aggregation of neurodegenerative proteins occurs in the gut at different stages of neurodegenerative diseases,[150,151] as well as in sporadic cases of IBD.[152] Protein aggregates are involved in several pathological events including degeneration of nerve fibers in the enteric nervous system (ENS) and activation of inflammatory response with expression of inflammatory cytokines.[153,154] Recent evidence demonstrated that endotoxin treated rodent are characterized by microglial activation, memory deficits and loss of brain synapses. Endotoxin promotes Aβ and tau aggregation. In the early stage of PD, intestinal permeability increases and mice treated with endotoxin showed α-syn overexpression and aggregation, as well as loss of dopaminergic neurons in the substantia nigra.[155]

Both α-syn and tau have been found as upregulated in the gut of patients affected by IBD. α-syn overexpression coincides with inflammatory response in the myenteric neurons of patients affected by CD.[156,157] Moreover, misfolded and aggregated α-syn occurs in the vermiform appendix of healthy individuals[158] and increases in the inflammed appendices.[159] Inflammation of vermiform appendix has shown a direct impact on the risk of developing PD.[160] Increased levels of tau isoforms and phosphorylated tau have been detected in the colonic mucosa and in the enteric plexus of CD patients, in relation to deregulated Nrf2/NDP52 pathway and decreased proteasomal degradation.[161]

In addition, dysbiosis can increase the production of bacterial amyloid fibers (Curli fibers), which can further act as seeding competent amyloid species for the aggregation of neurodegenerative proteins that, in turn, spread from the gut to the brain[162,163] (Figure 5).

The effect that cytokines and misfolded proteins produced in the gut have on the brain is under debate. Whether the nervous connection via the vagus nerve is responsible for the propagation of misfolded amyloid species from the gut to the brain, remains a challenging hypothesis, although the increasing number of evidence supporting this idea.[166,167] On the contrary, during chronic inflammation cytokines expressed in the gut could reach the brain toward the blood stream. Once in the brain, circulating cytokines might activate a cross-talk with astrocytes and microglia contributing to neurodegeneration. Several lines of evidences link systemic inflammation with the development of NDD. Serum and salivary levels of inflammatory cytokines are increased in patients with AD and PD, in comparison to healthy subjects[168–170] and clinical studies have reported the worsening of cognitive decline after sepsis or bacterial infections.[171,172] In accordance, animal models have highlighted the direct role of systemic inflammation and pro-inflammatory cytokines in driving neurodegeneration.[173,174] At this regard, it is worth of attention that targeting TRAF-2, though IRE-1α activation, induce NF-kappa B pathway and thus increase the expression of

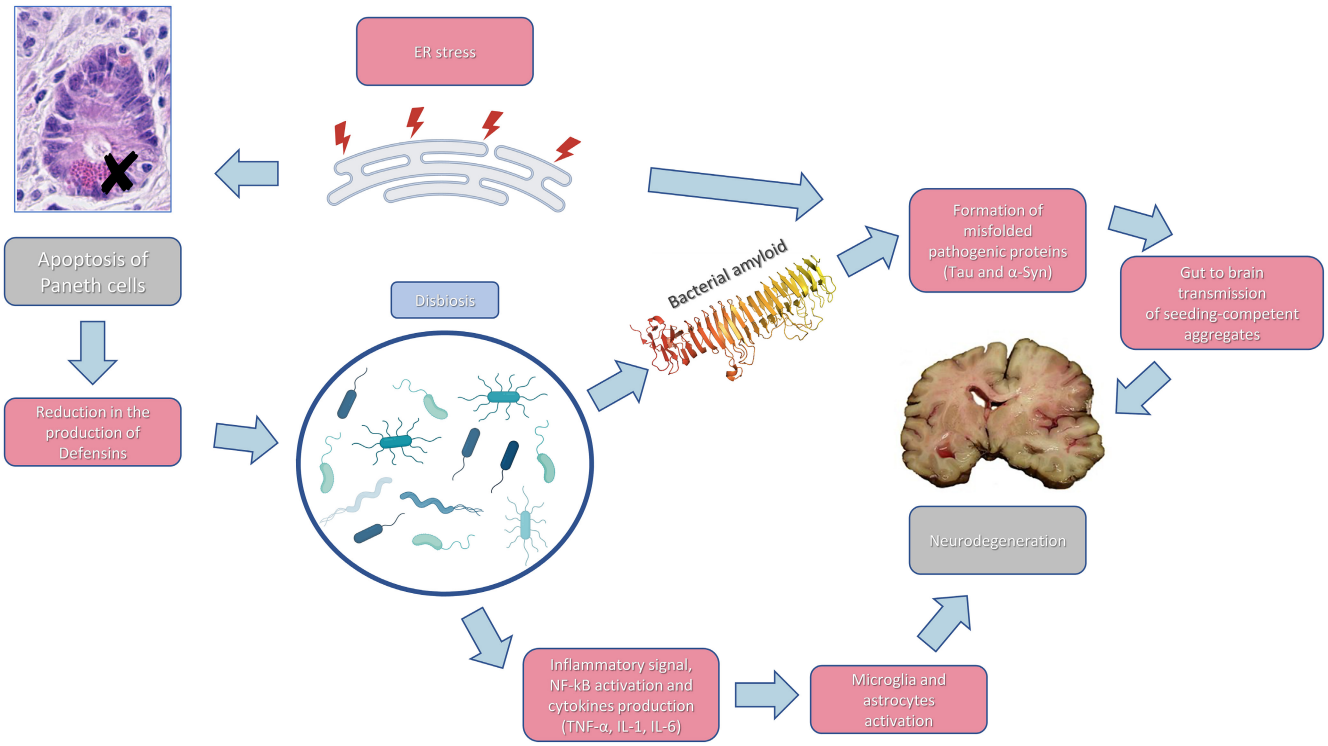

FIGURE 5 Schematic representation of the double-hit hypothesis by which ER stress can drive the development of neurodegeneration along the gut-to-brain axis, by promoting either the formation and the propagation of amyloid proteins as the production of pro-inflammatory cytokines and the microglia.[164,165]

inflammatory cytokines in the context of ER stress.[142,143] TRAF-2 is also directly responsive to TNFα. Recent evidence suggests that direct targeting of TRAF-2 by TNFα contributes to the development of neuroinflammation in course of AD[175] and that it can be involved in the apoptosis of neuronal cells, through the activation of c-Jun and JNK pathways.[176] Moreover, NLRP3 inflammosome in the nervous system can assemble in response to the activation of TLR4 by circulating LPS, promoting the transcription of pro-IL1β and pro-IL18.[156] These evidence support the hypothesis that inflammatory cytokines, produced in the gut in course of IBD, might be directly intertwined with ER stress and inflammation in the brain, contributing to the development of neurodegeneration.

Among the different neurodegenerative disorders, the gut to brain axis is more deeply investigated in PD. Accumulating evidence suggest that α-syn aggregates can spread from the brain to the periphery or from the gut to the brain, supporting a "dual-hit" hypothesis of PD.[177] Moreover, recent studies have also reported that EECs, which are exposed to the gut lumen and are in close contact with both enteric neurons and glial cells, express both tau and α-syn.[45,178] Due to their close anatomical connection with afferent nervous fibers, EECs might have a key role in the propagation of misfolded proteins form the gut to the brain, especially when subject to dysbiosis and ER stress.[179,180]

Inflammation of the gastrointestinal tract is a possible starting point of α-syn pathology and transmission since it has been considered the main factor responsible for cell-to-cell transmission of α-syn oligomers along the vagus nerve.[181] More interestingly, intriguing research has shown that inflammation of the intestine induced by sulfate-dextran is able to trigger the accumulation of α-syn pathology within the substantia nigra (SN) of mice.[182] These data have been also confirmed retrospectively in a postmortem cohort of patients affected by chronic IBD, in which aggregates of α-syn have been detected in both SN and dorsal striatum with a prevalence significantly higher comparing to sex- and age-matched controls.[183]

Indeed, the interaction between ER stress, production of inflammatory cytokines and dysbiosis might represent the interconnected pathway by which protein aggregates formed into the gut and transmit to the brain thought both vagus nerve and by bloodstream. Misfolded proteins, in fact, aggregate into β-sheet filaments and short β-sheet filaments are known to display prion-like properties,[184] enabling them to cell-to-cell transmission. Cytokines produced during bowel inflammation can act on neurons and microglia by direct activation of the NF-kB pathway, leading to neuroinflammation and propagation of misfolded proteins.[185]

Finally, an emerging role in this context would be related to lipid metabolism and the interplay between intestinal inflammation, lipid storage, and misfolded protein aggregation. IBD and intestinal inflammation are associated to an increased risk of liver steatosis and nonalcoholic fatty liver disease.[186,187] In turn, liver steatosis is associated to ER stress, mitochondrial dysfunction as well as accumulation of intracellular lipids droplets and misfolded proteins.[188,189] Although very few studies have explored the role of the liver in neurodegenerative disorders, it is important to underline that α-syn accumulates in the liver in course of PD, resulting in inflammatory infiltration and hepatocytes reorganization.[190] Moreover, 27-hydroxycholesterol (27-OHC)—a

cholesterol metabolite produced in the liver in course of hypercholesterolemia, aging, and oxidative stress that is able to cross the blood–brain barrier—has been reported to increase dopaminergic neuronal α-syn protein levels through inhibition of proteasomal degradation and decrease of the chaperone heat shock protein 70 (HSP70).[191]

In conclusion, ER stress has a key role in modulating a complex interplay between misfolded proteins, lipids homeostasis, and neuroinflammatory response. However, it is still unclear how these pathways could be connected to the intestinal alterations. Understand the involvement of ER stress in gut–brain axis during neurodegenerative disorders could provide new insights for the development of early biomarkers and the discovery of new therapeutic strategies.

AUTHOR CONTRIBUTIONS

Giorgio Vivacqua: Investigation; writing—original draft preparation; writing—review and editing. Romina Mancinelli: Conceptualization; investigation; writing—original draft preparation; writing—review and editing, funding acquisition. Stefano Leone: Writing—original draft preparation; writing—review and editing. Rosa Vaccaro: Investigation; supporting. Ludovica Garro: Revision curation; supporting. Simone Carotti: Investigation; supporting. Ludovica Ceci: Data curation. Paolo Onori: Conceptualization; editing. Luigi Pannarale: Visualization. Antonio Franchitto: Visualization; review. Eugenio Gaudio: Conceptualization; editing. Arianna Casini: Supervision, writing—original draft preparation; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created in this study.

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