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The Role of NF-κB in ER stress and its Pathological Implications

Bachelor's thesis in Biotechnology

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Abstract

The unfolded protein response (UPR) is activated by the endoplasmic reticulum (ER) with the purpose of recovering lost homeostasis due to ER stress. The three branches of this response: IRE1, PERK and ATF6 activate diverse transcriptional programs through different effector mechanisms in a context specific manner. Although UPR is primarily focused on ameliorating the stress produced by misfolded, unfolded or aggregated proteins in the lumen through its canonical activation, the response can change into a more aggressive approach if the initial attempts fail. In such a way, inflammatory pathways can be induced as an alarm that switches to apoptosis if the stress progresses up to an unbearable point for the cell.

The family of NF-κB transcription factors are key regulators of critical physiological processes and the chief effector molecules of UPR-induced inflammation. NF-κB can be activated by the three branches of the UPR and target inflammatory genes directed to control increasing apoptotic signals derived from an unmitigated ER stress. This relationship between inflammation and ER stress is critical for the understanding of several pathological conditions that exhibit both phenomena. Diabetes, cancer, cystic fibrosis or some neurodegenerative disorders are some examples of diseases where NF-κB and lost proteostasis converge to shape the observed symptoms and signs. Therefore, understanding the exact molecular mechanisms underlying this crosstalk is pivotal for the comprehension of several diseases. The elucidation of not only these pathways but the complex communication with other organelle compartments and their participation in the expression of a given disease is pivotal for generating efficient therapeutic programs. This work will present some insights into the current understanding of the mentioned routes and how they are involved in the progression of some diseases.

Key words: Endoplasmic Reticulum (ER), proteostasis, NF-κB, unfolded protein response (UPR), pathology

El Papel del NF-κB en el estrés del Retículo Endoplasmático y sus Implicaciones Patológicas

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Resumen

La respuesta a proteína desplegadas o mal plegadas (UPR en inglés) es activada por el retículo endoplasmático (RE) con el objetivo de recuperar la proteostasis perdida debido a estrés en el RE. Las tres ramas de esta respuesta: IRE1, PERK y ATF6 activan diversos programas transcripcionales a través de diferentes mecanismos efectores de manera específica al contexto. Aunque la UPR se centra principalmente en disminuir el estrés producido por proteínas mal plegadas, desplegadas o agregadas en el lumen a través de su activación canónica, la respuesta puede cambiar hacia aproximaciones más agresivas si los intentos iniciales fracasan. De esta manera, rutas inflamatorias pueden ser inducidas a modo de alarma que cambia a apoptosis si el estrés progresa hacia puntos no tolerables por la célula.

La familia de factores de transcripción de NF-κB son reguladores clave de procesos fisiológicos y moléculas efectores principales de la inflamación inducida por la UPR. NF-κB puede ser activado por las tres ramas de la UPR y activar genes que dirigidos a controlar las crecientes señales apoptóticas producidas por un estrés del RE no mitigado. Esta relación entre inflamación y estrés del ER es fundamental para la comprensión de varias patologías que exhiben ambos fenómenos. La diabetes, el cáncer, la fibrosis quística o algunas enfermedades neurodegenerativas son ejemplos de enfermedades en las que NF-κB y pérdida de proteostasis convergen para moldear los síntomas y signos observados. Por tanto, entender los mecanismos moleculares exactos subyacentes en esta interrelación es importante para la comprensión de muchas enfermedades. La elucidación de, no solo estas rutas, sino también de la compleja comunicación con otros compartimentos celulares y su participación en una enfermedad dada, es crucial para generar programas terapéuticos eficaces. Este trabajo presentará algunas ideas sobre el conocimiento actual de las rutas mencionadas y cómo están involucradas en la progresión de algunas enfermedades.

Key words: Retículo Endoplasmático (RE), proteostasis, NF-κB, respuesta de proteínas desplegadas (UPR), patología

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"Science, for me, gives a partial explanation for life. In so far as it goes, it is based on fact, experience and experiment" – Rosalind Franklin (1920-1958)

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Figures and tables

Abbreviations

ATF	Activating transcription factor
BiP	Binding immunoglobulin protein
CHOP	C/EBP homologous protein
eIF2	Eukaryotic translation initiation factor 2
EOR	ER-Overload Response
ER	Endoplasmic Reticulum
ERAD	ER-associated degradation
FAD	flavin adenine dinucleotide
FHC	Ferritin heavy chain
GADD	Growth arrest and DNA damage inducible protein
GRP	Glucose related protein
IkB	inhibitor of nuclear factor kappa B)
IKK	Inhibitor of nuclear factor Kappa B kinase
IL	Interleukin
IP3R	inositol-1,4,5-triphosphate (IP3)-receptor
IRE1	Inositol-requiring enzyme 1 a
JNK	c-Jun N-terminal kinase
MAPK	Mitogen-activated protein Kinase
MKP	MAP Kinase Phosphatase
MnSOD	Manganese Superoxide dismutase
NADP(H)	nicotinamide adenine dinucleotide phosphate
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NOS	Nitric Oxide Synthase
PERK	PKR-like endoplasmic reticulum kinase
ROS	Reactive Oxygen Species
RyR	Ryanodine receptor
TLR	Toll-Like Receptor
TNF	Tumor Necrosis Factor
TNFR	Tumor Necrosis Factor Receptor
TRAF2	TNFR-associated factor 2
UPR	Unfolded Protein Response
XBP1	X-box protein 1

Materials and Methods

The idea for this work was born from the curiosity that arises in a previous assignment about a rare neurodegenerative disease that exhibited a novel NF-κB signaling pathway in the context of a proteinopathy. The documentation process was carried out over a period of 3 months through intensive research, mostly in online databases of scientific literature such as Google Scholar, PubMed, Scopus, Web of Science, and ClinicalTrials. Previous knowledge of mentioned pathway was scarce, so an initial search covered wide aspects of the molecular biology surrounding its activation. In this sense, search terms such as "endoplasmic reticulum function", "unfolded protein response" or, "NF-κB AND endoplasmic reticulum" were used.

More than 200 000 articles appeared but one name was systematically repeated: Randal J. Kaufman. Several reviews from this author, published from 2002, were used as an introduction for further research. Key words were extracted from mentioned articles: "inflammatory response", "effector mechanisms", "apoptosis", "crosstalk", "mitochondria", "calcium signaling", "ROS production". These key words helped in the search for more specific aspects of the response. Article sieving was performed with the combination of terms, for example:

> "(NF-κB **OR** inflammation) **AND** (endoplasmic reticulum **OR** mitochondria) **AND** UPR"

Once a general idea was shaped, it was divided into different sections and investigated following the specific timelines of relevant discoveries and observations. For instance, "NF-κB **AND** UPR" led to Pahl & Baeuerle (1995) from which "ROS production", "antioxidants", "EOR", "calcium" were extracted. Later, "NF-κB **AND** ROS production **AND** calcium" led to Görlach et al. (2006) and then to several others up to Carreras-Sureda et al. (2018).

For the different sections of the work, some examples of the terms used are:

- UPR:
    - "UPR", "ERAD", "Endoplasmic Reticulum", "(IRE1-α **OR** PERK **OR** ATF6) **AND** UPR", "PERK attenuation of translation", "cellular proteostasis", "EOR", "EOR **AND** UPR", "Effector mechanisms of UPR", "NF-κB **AND** UPR", and other similar.
- NF-κB
    - "NF-κB signaling pathway", "canonical NF-κB", "IkBα dynamics in NF-κB inhibition", "IkBα physiological function", "IkBα molecular stripping", "alarming UPR **AND** NF-κB activation", "TLR **AND** UPR and NF-κB", and other similar.
- ER-stress, NF-κB and inflammation
    - "EOR **AND** ROS **AND** UPR", "inflammatory process induced by NF-κB", "ROS production during UPR", "ER stress **AND** ROS production", "ROS activation **AND** NF-κB", "NO **AND** NF-κB **AND** UPR", "mitochondria-ER crosstalk", "Calcium signaling in NF-κB activation", and other similar.
- Programmed Cell death
    - "UPR and apoptosis", "CHOP-mediated apoptosis", "ER-mediated apoptosis", "TNFα-induced JNK", "JNK-mediated apoptosis", "NF-κB **AND** JNK **AND** UPR", "NF-κB protective function under apoptotic stimuli", and other similar.

- Diseases
    - “UPR **AND** (disease **OR** pathology **OR** disorder) ”, “NF-κB and disease”, “neuroinflammation **AND** ER stress”, “diabetes and UPR”, “NF-κB activation in neurodegenerative disorders”, “clinical trials, neuroinflammation in neurodegenerative diseases”, “(cancer **OR** diabetes **OR** neurodegenerative disorder) **AND** (inflammation **OR** NF-κB) **AND** (UPR **OR** endoplasmic reticulum)”, “breast cancer **AND** UPR induction”, and other similar.

Furthermore, different reviews led to further looking into specific topics not only through the extraction of key words from the body of the article but also through references already used by some authors. The name of the studies was also used as guide for their selection, allowing a rapid discard of non-relevant works. Keywords found in the abstract also were key factors in the selection of a given paper. All in all, the 182 references used in this work are a compendium of reviews and specific studies focused on detailed features of the response of interest.

Introduction

The endoplasmic reticulum (ER) has a central role in lipid and protein synthesis. Its rough fraction, with attached ribosomes in its membrane, is responsible for the full translocation of proteins into the lumen (future lumenal proteins or destined for secretion) and partial translocation of transmembrane proteins (Alberts et al., 2002).

Protein synthesis is a major and extremely important process of cell activity and, given the diversity of protein populations present in a cell (varying in shape, size, secondary structure, post-translational modifications…), it is not surprising that several mechanisms exist at varying levels (protein, organelle, cell or tissue) to keep proteostasis (homeostasis of the proteome), understood as the maintenance of the balance between the building and turnover of proteins. Such mechanisms include the choice of codons, leading to an optimized translational rate, ubiquitination-mediated proteasome degradation or entire organelle-mediated responses such as the chaperon-assisted folding network activated by the unfolded protein response (UPR) among others already reviewed by Wolff, Weissman, & Dillin (2014). All these approaches render a highly effective machinery despite inevitable errors obtained due to the huge number of proteins required for cell's activity and survival (approximately 42×10^6 protein molecules/cell) (Ho et al., 2018).

Despite the amount of quality control mechanisms a cell has to ensure proteostasis is enormous, several conditions that disrupt ER homeostasis such as mutant proteins, disease or aging can lead to the accumulation of misfolded or aggregated proteins in the ER lumen, causing stress and potentially leading to cell death if the stress cannot be resolved (Hetz & Papa, 2018). In these cases, the cell activates the canonical UPR. Other dysregulated processes such as an excessive protein transport across the ER membrane during viral infection can also provoke stress and induced the UPR activation. In addition, the induction of these responses not only can be originated by the specific mechanisms of different diseases such as neurodegenerative disorders (Alzheimer's or Parkinson's disease among others), metabolic diseases, cancer and others**,** but also can contribute to their progression and pathological implications (Kaufman, 2002)

Interestingly, UPR is a very complex defense mechanism in communication with other compartments of the cell that allow the production of more elaborated and sophisticated responses. In this context, different and even contradictory transcriptional programs are started through the activation of diverse effector mechanisms and mediators to give response, in a more systemic way, to a variety of detrimental stimuli. For instance, inflammation is an often-observed effect under uncontrolled ER stress, which also seems to take part in the pathogenesis of several diseases (Grootjans et al., 2016; Xu, C. et al., 2005)

The loss of protein homeostasis is produced by several genetic, pharmacological insults or due to infectious processes. In this regard, the induction of ER stress, the severity of which determines the ultimate UPR mediated response, is used in cell and animal models to study several pathologies these insults give rise to.

This work is focused on the role of UPR upon the induction of ER stress and how it is able to generate the inflammatory process that accompanies the pathological states reached in different diseases. Specifically, the role of **NF-κB** as a consequence of the activation of this type of responses and how it is modulated exacerbating or diminishing the pathological implications of certain disorders.

UPR

The Unfolded Protein Response is an extensively studied mechanism that aims to maintain protein homeostasis in the cell. It is constituted by **three branches** that, when activated up-regulate different sets of genes related to the **folding machinery, pro-survival or pro-apoptotic** pathways. The **stimuli** capable of inducing UPR are very varied including **mutant proteins, protein aggregates, misfolded or unfolded proteins** (Hetz, 2012)**.** Along these lines, only correctly folded proteins can be delivered to Golgi apparatus to continue through the secretory pathway, kept in the lumen in the case of ER resident proteins or sent to membrane or other organelles if required (Alberts et al., 2002)

The **canonical activation** of UPR intends to alleviate ER stress produced by the accumulation of misfolded and unfolded proteins. The objective is achieved by increasing protein folding capacity through the targeting of genes coding ER-resident chaperone proteins such as BiP, GRP94, calreticulin or Erdj4. In order to do so, the UPR relies on the effector mechanisms **of three different sensor proteins**: **IRE1α, PERK and ATF6** (Mori, 2000) (Figure1.).

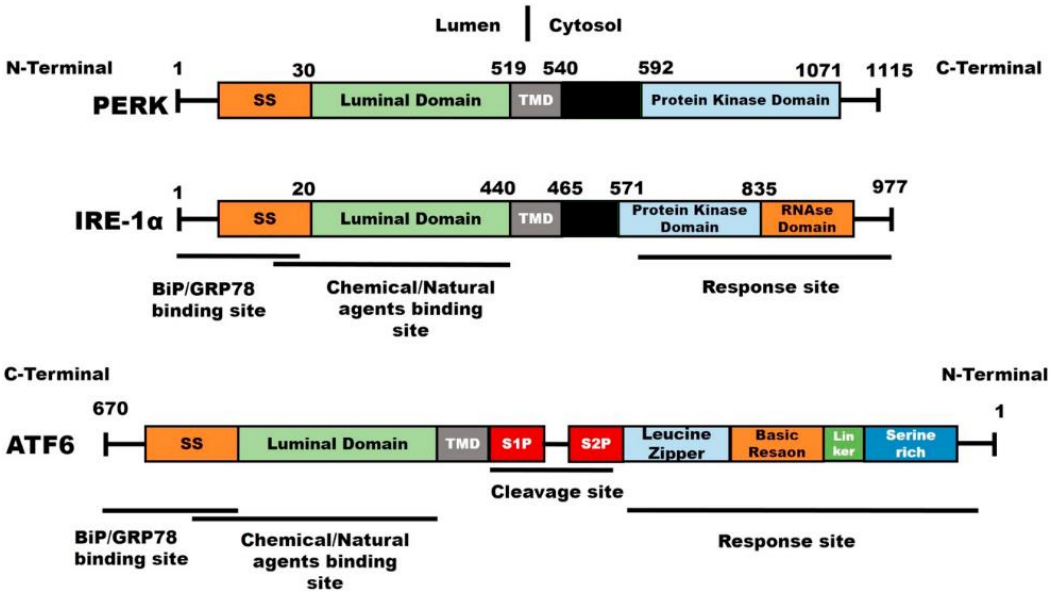

Figure 1. Structure of UPR sensor proteins: PERK, IRE1 and ATF6. The three sensors are transmembrane proteins with both luminal and cytosolic domains. PERK and IRE1 contain kinase domains that allow their autophosphorylation after di- or oligomerization. IRE1 has an additional RNase domain. ATF6 contains S1P and S2P cleavage sites. *Adapted from Pandey et al. (2019).*

UPR sensor proteins, under normal conditions, are attached to the ER-resident chaperone protein **BiP/GRP78**. BiP blocks the activation of the sensors, which remain in a monomeric form, **inactive**. When misfolded or unfolded proteins are present in the ER lumen, BiP dissociates from the sensors to bind to the aberrant proteins and start the folding process (Kaufman, 2002)**. If folding is not accomplished**, proteins are targeted for proteasomal degradation in the cytosol through a process called ER-Associated protein Degradation (**ERAD**) (Hwang & Qi, 2018). **Autophagy** or ER-phagy has also demonstrated to play an important role in the elimination of non-refolded proteins during ER stress (Smith & Wilkinson, 2017). In parallel, **IRE1α, PERK and ATF6 activate** and start different signaling pathways, induction of which is purposed to benefit the folding process through the up-regulation of

chaperone proteins. Together, UPR and degradation mechanisms aim to restore homeostasis in the ER lumen (Hwang & Qi, 2018).

Canonical response

IRE1α

The serine/threonine-protein kinase/endoribonuclease **inositol-requiring enzyme 1 α** (IRE1α) is a type I ER transmembrane protein containing three different domains: one lumenal domain (N-terminal sensor) and two cytosolic domains, one serine-threonine kinase domain and one RNase domain (Kaufman, 2002). After dissociating from BiP, it dimerizes and trans-phosphorylates through its kinase domain, activating, in this way, the RNase domain (Fig.1). The activation of its RNase activity leads to the splicing of the X-box binding protein mRNA (**XBP1**). Cleavage of XBP1 mRNA delivers the transcription factor XBP1s, which allows the transcription of genes related with protein folding (mainly chaperones), secretion, lipid synthesis, pro-inflammatory responses or ERAD (Kaufman, 2002)(Fig. 2).

PERK

PERK or protein kinase RNA (PKR)-like endoplasmic reticulum kinase, is structurally related to IRE1α, but lacks RNase domain (Fig.1) and is activated in a similar way, it auto-phosphorylates. However, its effector mechanism is different. PERK activation aims at halting global protein synthesis.

For starting translation initiation, a ternary complex must be formed by the eukaryotic translational initiation factor 2 α (**eIF2α**) complex, Met-tRNA and GTP (Holcik & Sonenberg, 2005; Proud, 2005). Later, the small ribosomal subunit is assembled. The eIF2α complex is loaded with GTP, which must be hydrolyzed, once the start codon is encountered, in order to release the nascent peptide from the ribosome. Upon hydrolyzation, the complex frees **eIF2α-GDP** from the ribosome. Further input of amino acids requires the recycling of eIF2α-GDP to eIF2α-GTP. This process is carried out by **eIF2β**, a guanin nucleotide exchange factor (Proud, 2005).

Unlike IRE1α, PERK does not cleave an mRNA but instead phosphorylates eIF2α in Ser51. When eIF2α is phosphorylated it can no longer act as a substrate for eIF2β and recover its GTP-loaded form. Instead, it becomes an eIF2β inhibitor, suppressing protein translation due to the impossibility of further adding amino acids to the nascent peptide chain (Holcik & Sonenberg, 2005). This strategy allows the cell to recover from ER stress without having to deal with sustained protein synthesis which, in these kinds of situations, becomes incompatible with cell survival. Phosphorylation of eIF2α may occur in conditions different to those of the UPR. Four different kinases can play this role depending on the stimulus: infection (double-stranded RNA-dependent protein kinase **PKR**), heme-depletion (heme-regulated inhibitor, **HRI**), amino acid starvation (general control non-depressible 2, **GCN2**) or unfolded proteins in the ER (**PERK**) (László & Wu, 2009). Just like PERK, the other three kinases also have links to ER stress but can function independently of it too.

Translational attenuation is a transient effect. Therefore, after the homeostasis is recovered, several genes are upregulated to reverse eIF2α phosphorylation through protein phosphatase 1 (PP1). In order to do so, ATF4, a transcription factor directed and preferentially transcribed by PERK during ER stress, upregulates GADD34 (growth arrest and DNA damage-inducible protein), a PP1 regulatory subunit which recruits PP1 to dephosphorylate eIF2α (Novoa et al., 2001)(Fig.2). Interestingly, this observed phosphorylation/dephosphorylation cycle is found to be impaired in cancer (Silvera et al., 2010).

ATF6

ATF6 is a type 2 ER transmembrane bZIP transcription factor. Upon activation, it travels to the Golgi apparatus via protein COPII-covered vesicles where undergoes intramembrane proteolysis by S1P (serine protease site-1) and S2P (metalloprotease site-2), releasing its cytosolic domain. This selective cleavage transforms ATF6 into an active transcription factor: **pATF6α(N)** (Schindler & Schekman, 2009) **pATF6α(N)** acts synergistically with XBP1s to induce several UPR target genes. Some folding related genes activated by ATF6 are: BiP/GRP78, endoplasmin/GRP94, CHOP/GADD153 and XBP1 (Fig.2).

Adaptive, alarming and apoptotic UPR

UPR is, indeed, not a single static response but its effects are modulated depending on the context: type, intensity and duration of the stimulus, cell type and other underlying conditions. Altogether, these parameters are able to switch the UPR outcome from pro-survival to pro-apoptotic effect. All in all, a total of three described effector mechanisms induced by the UPR have been observed: adaptive, alarming and apoptotic (Kim, I. et al., 2008). Generally, upon mild stress, **adaptive** or **canonical UPR** is activated with the purpose of up-regulating chaperone proteins to start the folding process and go back to a homeostasis, a response already discussed here (Fig.2). Also, at this stage, if proteins cannot be refolded, other related machineries such as ERAD and ER-phagy are initiated in order to alleviate the stress provoked (Hwang & Qi, 2018; Smith & Wilkinson, 2017). In fact, XBP1s targets genes coding ERAD components, suggesting and interplay between ERAD and **IRE1α** (Hwang & Qi, 2018).Further in time, if stress is not resolved, the cell activates pro-apoptotic programs leading to cell death.

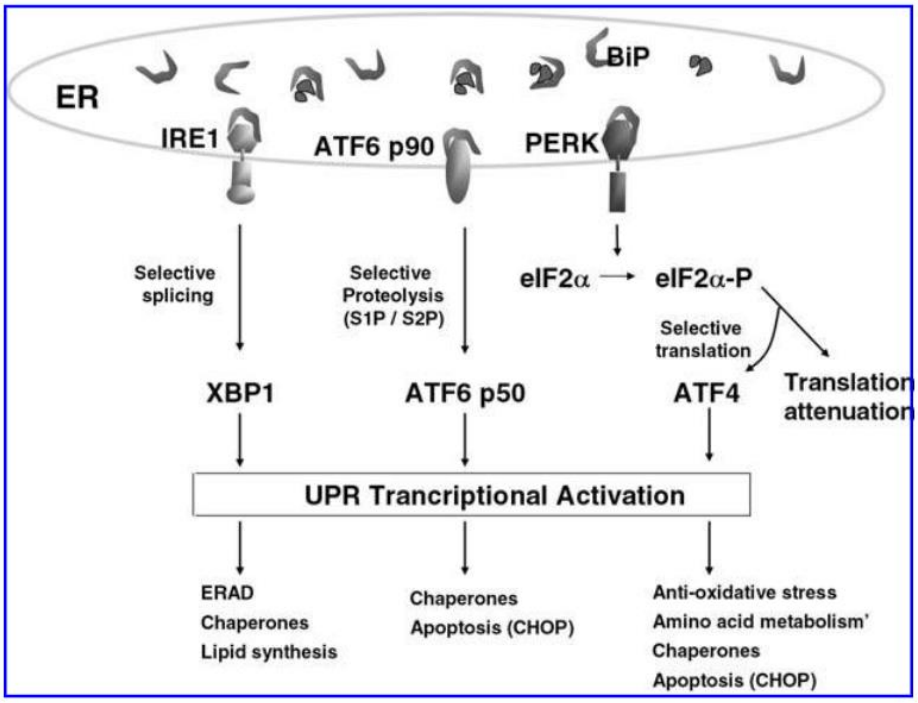

Figure 2. The canonical UPR response aims to restore protein homeostasis through the induction of genes related with folding machinery, such as chaperone proteins, and ERAD or ER-phagy degradation mechanisms. *(Malhotra & Kaufman,2007)*.

Apoptotic UPR

Opposing to the adaptive mechanism, the **apoptotic** or **terminal** UPR activated under severe or chronic stress.

Some apoptotic signals induced by the UPR include the strong activation of C/EBP homologous protein (**CHOP**/**GADD153**) by **PERK**, **ATF6** and **IRE1α**, Bak/Bax-regulated Ca^{2+} efflux from the ER, IRE1-mediated activation of the ASK1/JNK pathway or cleavage and activation of procaspase-12 (Malhotra & Kaufman, 2007). CHOP can be activated in different scenarios: when the transcription factor ATF4 binds to the AARE1 and AARE2 ER stress responsive transcriptional enhancer elements, upon binding of XBP1s to ER stress response element (ERSE) or when the ATF6 active form binds to ERSE (Crysovalantou et al., 2016). Nevertheless, PERK-eIF2α-ATF4 axis seems to be the main source of CHOP since its induction is almost totally prevented in PERK null cells (Harding et al., 2000). However, it is also worthy to point out that according to a very recent study using an ordinary differential equation model coupled with high-throughput confocal imaging, ATF6 appears to have also a pivotal role in the initial phases of pro-apoptotic CHOP during ER stress and in later phases to shape its dynamics (Yang et al., 2020). All these strategies tend to up-regulated CHOP, which plays a critical role in the apoptotic process. In fact, it has been demonstrated that $CHOP^{-/-}$ cells are resistant to apoptosis (Zinszner et al., 1998). This transcription factor targets several pro-apoptotic proteins such as BH_3-only proteins, BID, BIM, NOXA or PUMA (Volkmann et al., 2014, Galehdar et al., 2010). Furthermore, Bcl-2 anti-apoptotic proteins are downregulated under the expression of CHOP (McCullough et al., 2001), which also restores protein synthesis through GADD34-PP1. The reverted attenuation of translation through eIF2α dephosphorylation cannot be sustained by the cell, which, hence, commits to die (Urra et al., 2013).

On the other hand, IRE1α organizes into higher order oligomers and interacts with TNF receptor (TNFR)-associated factor 2 (**TRAF2**). This interaction allows the activation of the Apoptosis Signal-regulating Kinase 1 (**ASK1**)/c-Jun NH_2-terminal kinase (**JNK**) pathway which, in the end can regulate the mitochondrial or intrinsic apoptotic pathway (Urano, 2000). Additionally, IRE1α starts a promiscuous RNA degradation process called RIDD (Regulated IRE1-Dependent Decay). Its RNase domain acquires affinity for ER-resident mRNA, miRNA and rRNA plus other substrates leading to a depletion of ER cargo and protein-folding components which, in turn, worsens ER stress (Maurel et al., 2014).

Bax pro-apoptotic protein is translocated to mitochondria, triggering apoptosis (Xu, C. et al., 2005). And, since UPR is a highly energy-consuming process, under unsolved ER stress, the three sensors IRE1 α, PERK and ATF6 start apoptotic programs, in a cooperative manner, as an ultimate mechanism for energy saving. Interestingly, the formation of reactive oxygen species (ROS) as a result of prolonged ER stress, described in following sections of this work, also contributes to apoptosis in an ER-mitochondria cooperative manner.

Figure 3 schematizes all this process, also adding some other participants which will be object of this work later on.

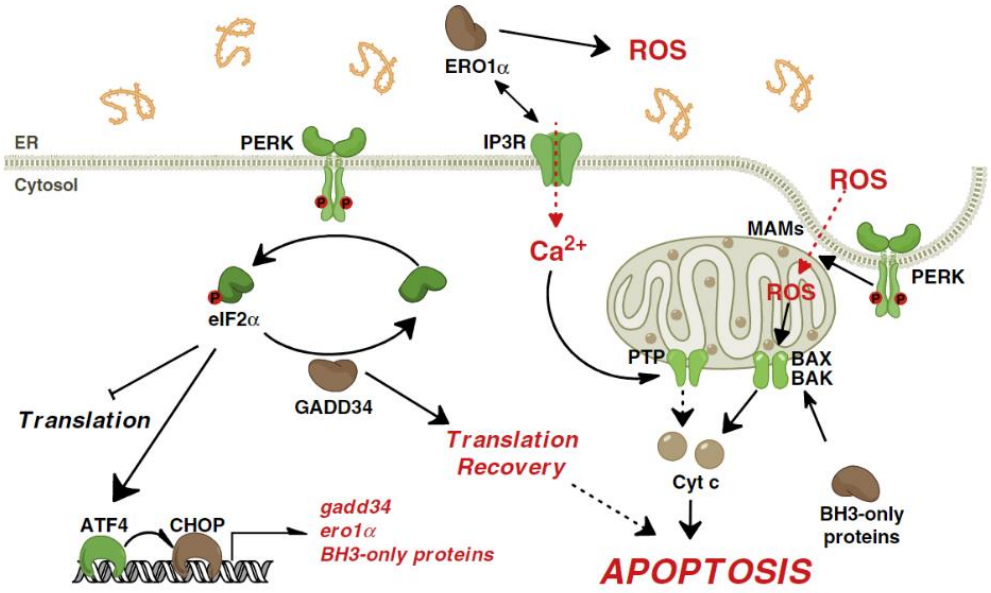

Figure 3. Apoptosis can be achieved through several pathways. PERK's preferential transcription of ATF4 leads to CHOP expression. It transcribes GADD34, ero1α, BH3-only proteins, among others. Translation halt can be reversed through dephosphorylation of eIF2α by GADD34. Translation recovery under ER stress is not sustainable for survival. Ero1α sensitizes of IP_3R but also participates in the production of ROS in a mitochondria-independent manner. ER Ca^{2+} efflux provokes the mitochondrial membrane release of Cytochrome C (cyt c) starting apoptosis. BH3-only proteins and ROS further act of bak/bax leading to further cyt c release and apoptosis. This apoptotic network downstream CHOP expression can also be started by IRE1 and ATF6 although said pathways are not depicted in the figure. In addition, CHOP is not the only apoptotic pathway linked to UPR. IRE1-derived ASK1/JNK activation NO and ROS production, also have pivotal roles in ER stress-induced apoptosis. MAMs: Mitochondria-Associated ER Membranes, PTP: mitochondrial Permeability Transition Pore. *Urra et al. (2013*

Alarming UPR

Nevertheless, there is one more effector mechanism induced before the apoptotic fate of the cell is decided. If folding capacity of the cell is overwhelmed by the ER-stress, the cell induces the **alarming UPR. NF-κB** along with other pro-inflammatory pathways, such as **JNK or p38 MAPK**, are activated to up-regulate a diverse variety of target genes supposed to lead the cell back to the homeostasis (Kim, I. et al., 2008)

Cells start an inflammatory process, which in turn, can promote the activation of a tissue-wide response. UPR involvement in the life cycle of immune cells is emphasized, for instance, in B cells, which require intact UPR mechanisms in order to become plasma cells. This UPR dependency is explained by the fact that plasma cells are characterized by having a massive secretory efflux of proteins due to their capacity of antibody production (Wu & Kaufman, 2006).

Along these lines, cells secreting high amounts of proteins such as hepatocytes, β cells or glial cells require highly developed secretory pathways. The fact that this process is largely dependent on the ER function, causes greater susceptibility to ER stress. Therefore, these cell types are often observed to be involved in the pathology of diverse diseases (Garg et al., 2012). The variety of cell types shown to participate in these disorders through the promotion of UPR, accounts for the diversity of responses proposed to be exhibited upon the induction of ER stress. In this context, inflammation is often developed as a consequence of unresolved ER stress, and often observed to accompany the mentioned diseases. At the molecular level, UPR-mediated **NF-κB pathway** has been proved to be a

main character in the generation of feed-forward inflammatory processes exacerbating the pathology of e.g.: neurodegenerative disorders (Lanzillotta et al., 2015). Ultimately, if the unresolved stress further progresses into a non-bearable process, the effector mechanisms producing an inflammatory process switch to execute apoptotic transcriptional programs, provoking cell death.

NF-κB

Nuclear factor kappa-light-chain-enhancer of activated **B**cells (**NF-κB**) is a family of transcription factors formed by 5 different proteins belonging to the Rel Homology Domain (RHD) containing family: p65 (RelA), RelB, c-Rel, p105/p50 (NF-κB1) and p100/52 (NF-κB2). RHD is composed by 2 Ig-like barrel subdomains connected by a flexible linker. The N-terminal domain ensures NF-κB binding to DNA at the level of the major groove. The C-terminal domain is in charge of dimerization and contains inhibitory interfaces (Hayden & Ghosh, 2012).

The family is involved in the mediation of inflammatory, immune and stress responses but also in regulation of apoptosis, proliferation and differentiation of immune cells. The different members combine to generate homo- or hetero-dimeric complexes, being the most abundant **RelA(p65)/p50.** Following the RHD, **NF-κB** possesses a nuclear localization signal (NLS) granting its nuclear translocation when it is exposed. However, only three of the members (RelA, RelB and c-Rel), are synthesized as already mature proteins and contain transcription transactivation domains (TAD) responsible for activating **NF-κB** target genes (Zhang, Q. et al., 2017). In contrast, p50 and 52 are obtained by proteolytic cleavage of the C-terminal portion of their respective precursors p105 and p 100. Since p50 and p52 do not contain TADs, homodimers of these components do not act as activating transcription factors but rather as inhibitors regulating **NF-κB** activity. The variety of dimer combinations might lead to a distinct affinity for **κB promoter variants,** accounting for the modulation of very distinct transcription programs.

Canonical activation of NFkB

NF-κB is canonically activated as a result of the stimulation of cytokine receptors such as TNFR, IL-1R or TLR-4 and antigen and pattern recognition receptors. Alternative pathways involving CD40 ligand or B cell activating factor (BAFF) can also induce **NF-κB** activation. Hence, different inducers such a pro-inflammatory cytokines, TLR or antigen receptor ligands signal through different receptors and adaptors but still, all pathways converge at the level of the IKK complex (Zhang, Q. et al., 2017; Mathes et al., 2008).

NF-κB is normally found sequestered in the cytoplasm by different inhibitors comprising the IkB family: **IkBα, IkBβ, IkBε, IkBNS, IkBz, BCL-3** and the C-terminal regions of the precursors p100 (**IkBδ)** and p105 (**IkBγ).** Nevertheless, **IkBα** is the canonical p65/p50 inhibitor and it is constitutively expressed (Fortmann et al., 2015).

Aside from covering the NLS, **IkBα** participates in **NF-κB** retention through its nuclear export sequence (NES). NES is also needed to return NF-κB to the cytosol from the nucleus after it has performed its function. According to Mathes et al., (2008), **IkBα** exists in two forms in the cell: free and bound to **NF-κB. NF-κB-bound IkBα** is stable, with a half-life of 8 to 10 hours; while free **IkBα** is a more unstable form, with a shorter half-life of 10 to 20 minutes. The difference in degradation rate is due to an **IkBα**

conformational change occurred upon binding to **NF-κB. IkBα** is composed by six N-terminal ankyrin repeat (AR) domains (conserved serine residues) and a C-terminal PEST sequence. As a consequence of binding to **NF-κB**, **IkBα** suffers a conformational change that affects some of these AR, yielding a much more stable structure. Lower stability of free **IkBα** accounts for a more rapid proteasome-dependent degradation without the need for previous ubiquitination Mathes et al., 2008) On the other hand, the more stable **NF-κB-bound IkBα** requires a ubiquitin-dependent process to be degraded (Ramsey et al., 2017; Dembinski et al., 2017;Ramsey et al. ,2017). Degradation of **NF-κB-bound IkBα** frees **NF-κB** from its inhibitor allowing its translocation to the nucleus. This occurs when **IkBα** is phosphorylated in Ser32 and Ser36 by **IkB kinase (IKK)**, a complex composed by three subunits: IKKα, IKKβ and IKKγ (**NEMO**), which oversees the process (Zhang, Q. et al., 2017). Later, **IkBα** is polyubiquitinated and targeted for proteasomal degradation. When **NF-κB** is released, the NLS is unmasked and the transcription factor is available for nuclear translocation. Once in the nucleus, **NF-κB** binds to consensus **κB** promoter sites and transcribes its target genes: cytokines, chemokines, adhesion molecules or inhibitors of apoptosis (Xia et al., 2001). However, **NF-κB** activation and subsequent translocation is supposed to be transient, otherwise its sustained activity could carry fatal consequences to the cell. Therefore, the activation of **NF-κB** must be tightly controlled. One target gene of **NF-κB** is its own inhibitor, **IkBα** which, after synthesis, travels to the nucleus and binds to **NF-κB-DNA** through its short C-terminal PEST (proline, glutamate, serine, and threonine) sequence, establishing a ternary complex. Negative charges from the PEST sequence repel negatively charged DNA and takes **NF-κB** off in a process called molecular *stripping* (Dembinski et al., 2017). **IkBα** takes **NF-κB** back to the cytoplasm where they remain until further stimuli provoke **IkBα** phosphorylation by IKK and the cycle is repeated. Altogether, **IkBα** plays a critical role in the regulation of **NF-κB** activation through a negative feedback loop. Inhibition of non-canonical **NF-κB** complexes such as RelB/p52 works slightly different to the canonical RelA/p50 inhibitory mechanism and are activated through alternative pathways (Pahl & Baeuerle, 1995) (Fig.4).

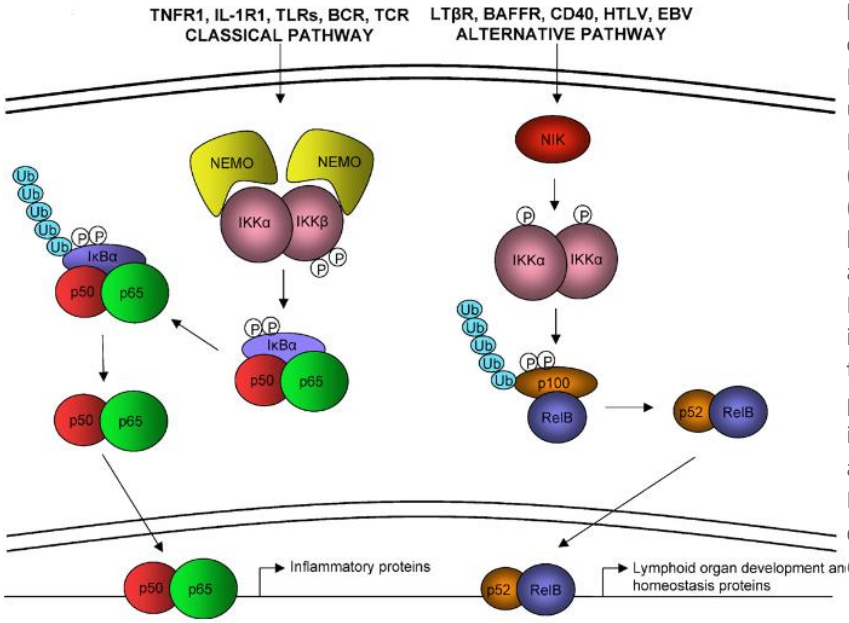

Figure 4. Classical pathway of NFkB activation relies on IKK phosphorylation of IkBα upon stimulation of TNFR1, IL-1/TLR, T-cell receptor (TCR) and B-cell receptor (BCR) with corresponding ligands. This pathway activates the canonical NFkB, which transcribes inflammatory proteins. On the other hand, alternative pathways are IKK-independent and aim to activate non-canonical NFkB complexes with differential functions. *Gloire et al. (2006)*.

Although **NF-κB** pathway is extensively studied in the context of adaptive immune responses e.g. promoting lymphocyte proliferation or antibody production; it can also be induced through immune-independent mechanisms. Early in the study of **NF-κB pathway,** it was described that ER stress-inducing drugs such as thapsigargin and tunicamycin showed **NF-κB** activation (Jiang et al., 2003). Considering the early descriptions of the UPR, it was not surprising that the activation of **NF-κB** as a consequence of ER stress inducers was first seen as a UPR-independent pathway. However, we currently know that all three UPR sensors contribute to **NF-κB** activation in the context of the alarming UPR, which triggers the expression of genes related to inflammatory processes. Under these circumstances **NF-κB** might be a chief inflammatory mediator in UPR-related pathologies where inflammation is part of the etiopathogenesis.

UPR-dependent NF-κB activation

The three UPR branches are able to induce the activation of **NF-κB** pathway, although through different mechanisms (Tam et al., 2012; Yamazaki et al., 2009). Under ER stress, PERK dimerizes, transphosphorylates and activates, promoting, among others, the activation of **p65/p50** complex in cells treated with thapsigargin (Jiang et al., 2003). This observation is supported by Deng et al. (2004) work, since this effect is suppressed either using PERK-lacking MEFs or with a S51A eIF2**α** mutant, which abolishes the PERK1 phosphorylation site. In addition, PERK was required for the expression of a luciferase reporter driven by kB promoters. Jiang et al. (2003). Deng et al. (2004) concluded that, as discussed before, PERK kinase activity induces phosphorylation of eIF2α. Translation attenuation is induced and free **IkBα** is rapidly depleted. However, under these circumstances the more stable **NF-κB-bound IkBα** remains unaffected. During these experiments, neither Zhang & Kaufman (2008)or Tam et al. (2012) observed activation of IKK, suggesting the existence of a non-canonical pathway for **NF-κB** induction in dependence of PERK activation. In a posterior review of the topic, Zhang and Kaufman (2008) states:

> "*Because the half-life of IkB is much shorter than that of **NF-κB,** attenuating translation increases the **ratio** of **NF-κB to IkB,** thereby freeing **NF-κB** to translocate to the nucleus in response to ER stress*"

This and posterior work stablish the existence of a basal production of NF-κB components which, under normal conditions would be held by **IkBα** in the cytosol but, upon **IkBα** decay due to PERK-mediated translation halt, would outnumber the inhibitor and translocate to the nucleus. However, according to (Ramsey et al., 2017) **NF-κB** is fully activated only in IRE1α competent cells. They prove that IRE1α is required for the maintenance of IKK basal levels, which are sufficient and necessary for **NF-κB** activation. PERK, on its own, is incapable of inducing a significant amount of **NF-κB** release, as observed in IRE1$^{-/-}$ cells, due to a reduced amount of IKK basal levels (Fig. 5.).

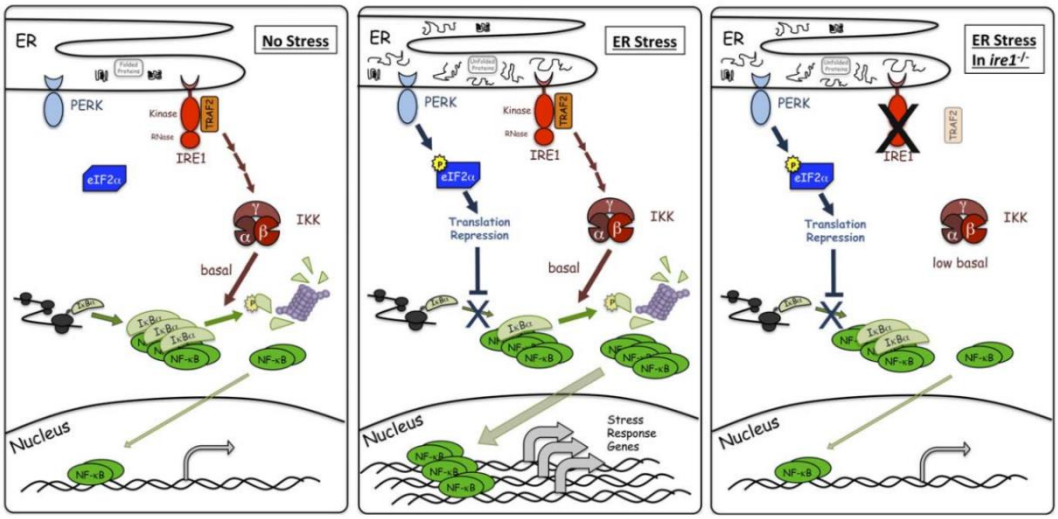

Figure 5. Under unstressed conditions, IkBα is synthesized and inhibits NF-κB. Through IRE1-TRAF2 complex, IKK basal activity is maintained, being sufficient to phosphorylate IkBα for its proteasomal degradation. A minimal amount of NFkB expression is observed. Under ER stress, PERK attenuates protein synthesis, accounting for degradation of free IkBα. Alongside IRE1, both participate in the degradation of IkBα for NFkB release. IRE1 role in this process is evaluated in IRE1$^{-/-}$ cells, where NFkB expression is considerably reduced even under ER stress. All this suggest a cooperation of IRE1 and PERK in the activation of NFkB and a dependency of IRE1 for fully initiating its transcription under these circumstances.

The importance of IRE1 in **NF-κB** activation is mediated by IKK. As already discussed, it acquires the role of being the convergent point between the large variety of pathways triggering canonical activation of **NF-κB**. Under unresolved ER stress, **IRE1α** oligomerization increases, determining the switch from an adaptive to an alarming or even an apoptotic response (Yamazaki et al., 2009). Hyperactivation of IRE1α allows the recruitment of tumor necrosis factor receptor (TNFR)-associated factor 2 (TRAF2), a ubiquitous adaptor protein also found in the TNFα- and TLR-mediated activation of **NF-κB**, as well as **MKP8/JNK pathways** Zhang et al. (2006). Next, IRE1α and TRAF2 complex permits **IKKβ** and IRE1α indirect communication through **IKKβ** binding to TRAF2. Then, **IkBα can be** phosphorylated by **IKKβ** and successively degraded. All in all, authors propose that collaborative work between PERK and IRE1α is, indeed, mediating **NF-κB** activity modulation as a consequence of ER stress. Therefore, while PERK allows free **IkBα** decay promoting **NF-κB** release, **IRE1α** could direct **NF-κB-bound IkBα** degradation through phosphorylation and posterior ubiquitination, enhancing the response.

The participation of ATF6 in **NF-κB** activation during ER stress is not as prominent as the involvement of PERK and IRE1α. However, the Shiga strain of *E.coli* produces subtilase cytotoxin, a protease able to degrade BiP, provokes phosphorylation of Akt which starts the **NF-κB** signaling pathway through the ATF6 branch of the UPR (Cray et al., 2009) .However, the links of ATF6 with inflammation extend to the induction of events leading to the acute-phase response (APR), a systemic inflammatory process (Martinon et al., 2010)observed that, in liver, CREBH, a bZIP-containing transcription factor and tissue specific UPR sensor similar to ATF6, and ATF6 dimerize and act synergistically for the transcription of APR genes (APPs). This response is activated in early stages of the innate immune response triggered by pro-inflammatory cytokines such as IL-1, IL-6 and TNF, experimentally proven targets of **NF-κB** (Heike L. Pahl & Baeuerle, 1997; H.L. Pahl & Baeuerle, 1995).

TLRs: Other pathways cross-talking with UPR for NFkB activation

Alarming UPR is associated to inflammation by the fact that activated pro-inflammatory pathways such as **NF-κB,** among others, are triggered during ER stress. These pathways primarily target genes involved in the establishment of inflammatory environments: cytokines, chemokines, … Importantly, UPR-mediated activation of **NF-κB** and consequent production of pro-inflammatory cytokines can signal in an autocrine fashion by stimulating TLR pathways (Hu et al., 2006). This states a clear UPR-to-inflammation flow of events, also exemplified by the fact that XBP1s is known to target genes encoding various cytokines. However, such relationship between UPR and inflammatory pathways is also apparent in the opposite direction: from inflammation to UPR. For instance, TLRs can stimulate IRE1α-mediated splicing of XBP1 mRNA in mouse macrophages Davies et al. (2009). Considering all this, UPR concomitant activation appears to enhance TLR responses (Kim, S. et al., 2018). This evidence points out to a complex intercommunication between UPR and different cell signaling routes. Indeed, upon stimulation of tunicamycin, an ER-stress inducer drug, pre-treated macrophages with high concentrations of LPS, cells strongly activate **NF-κB** pathway but, when LPS was present in low concentrations, cells induce CHOP and ATF4 expression (Woo et al., 2009, 2012).

To summarize**, NF-κB** activation as a consequence of the UPR mainly follows the interplay between PERK and IRE1α with the exception of the few exceptions in which ATF6 was also shown to contribute. PERK supports the depletion of free **IkBα** by stopping the transcription of **IkBα** gene (*NFKB1A*) while IRE1α allows further activation of **NF-κB** by inducing IKK activity over pre-existing **NF-κB**-bound **IkBα.** However, it is worth highlighting the diversity of possible **NF-κB** complexes and their specific modulatory dynamics which may or not qualitatively differ from the canonical regulation of **NF-κB** activation. Yet, the intricacy of **NF-κB** signaling mechanisms does not stop there but increases with the crosstalk with other pro-inflammatory pathways which, in turn, also communicate with UPR. In this sense, the inflammatory phenotype induced by the UPR, which involves the activation of **NF-κB,** but also JNK, p38 and other pathways, is essential for innate immune response (Fig.6). All these routes regulate the expression of pro-inflammatory genes potentiating cell-survival in a context-specific manner. On the other hand, several pathological conditions in which ER stress is present also show UPR activation and, overtime, inflammation. However, in most of them, the exact correlation between both observed phenomena is not yet elucidated, sometimes suggesting more intricate mechanisms for the underlying cause of the condition. Along these lines, it must be mentioned how not only unfolded, misfolded or aggregated proteins can cause the induction of ER stress. Other environmental insults such as the depletion of Ca^{2+} in the ER lumen, alteration of RedOx status, energy (sugar/glucose) deprivation or altered posttranslational modifications can also lead to the activation of the UPR (Carreras-Sureda et al., 2018; Görlach et al., 2006; Malhotra & Kaufman, 2007) All these new elements shape a much more sophisticated response involving other cellular compartments such as mitochondria and the participation of the UPR-independent kinases responsible for eIF2α phosphorylation. This very complex response is known as Integrated Stress Response (ISR), the effects of which contribute to the worsening of ER stress and probably to the switching from an adaptive to an alarming response entailing the activation of **NF-κB.**

The crosstalk between UPR and NF-κB described in previous paragraphs is depicted in Figure 6 along with other inflammatory pathways induced by the UPR.

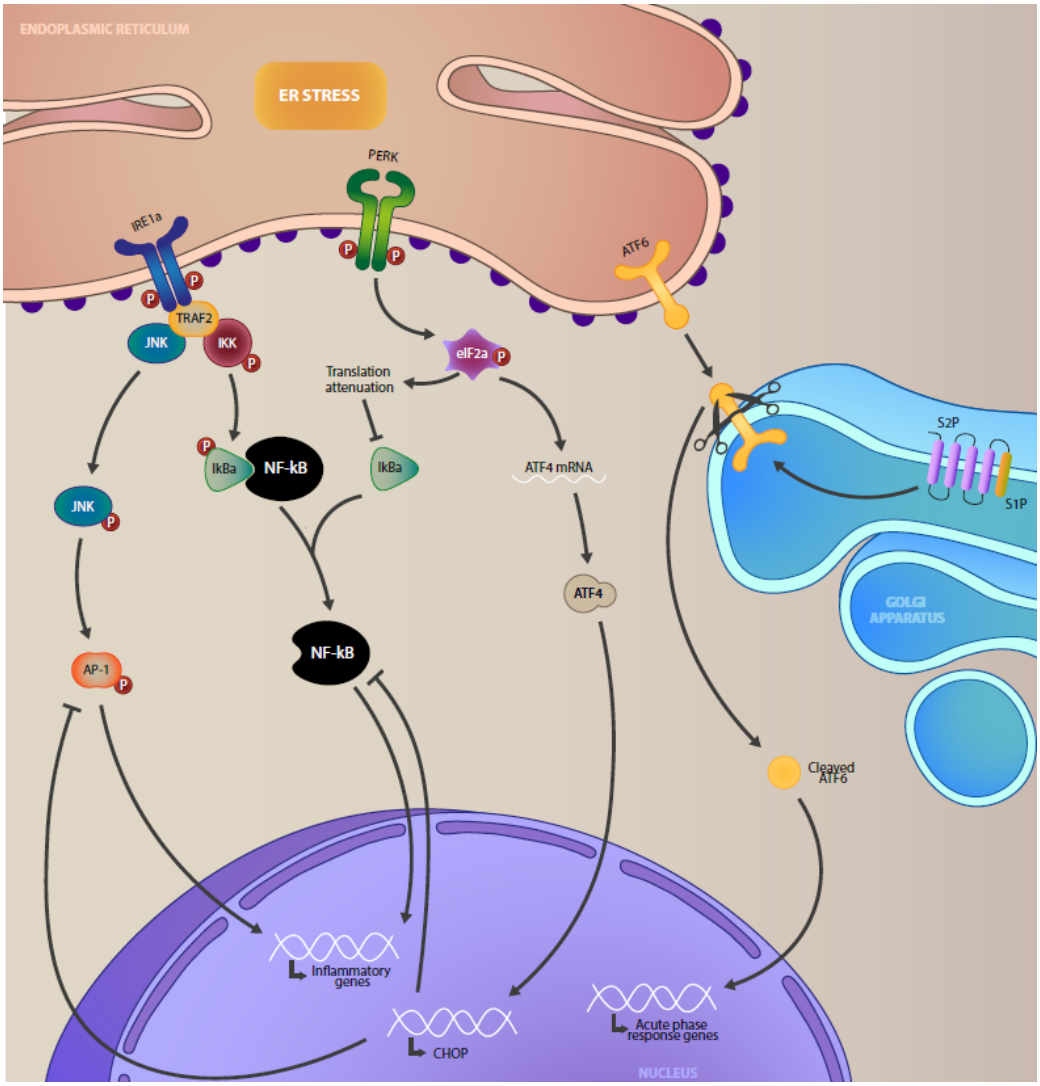

Figure 6. UPR-derived inflammatory pathways. IRE1α-TRAF2 complex couples with JNK and IKK to induce both AP-1 and NF-κB inflammatory pathways. NF-κB activation is also promoted by degradation of free IkBα during protein translation induced by PERK activity. Additionally, PERK's preferential transcription of ATF4 mRNA leads to the expression of CHOP. Cleaved ATF6 translocates to the nucleus and starts the transcription of acute phase response genes. Altogether, the different pathways shape a complex inflammatory process inside the cell.

EOR: a UPR-dependent pathway

Principally, the three UPR sensors, IRE1α, PERK and ATF6 work purposefully together to ameliorate ER stress produced by misfolded, unfolded, mutated, or aggregated proteins. However, aberrant protein folding and/or aggregation are not the only cause for activation of the UPR. An excessive transport of proteins across the ER membrane can also provoke ER stress. Exaggerated protein efflux produces ER membrane distension, a phenomenon often observed in viral infections due to the massive viral protein production that overwhelms the secretory pathways of the cell. Under these conditions, the cell induces a sometimes described as a "*UPR-independent stress response*" named **ER-overload response** (EOR). The EOR is defined as Ca^{2+} dependent and relies on the activation of **NF-κB** (Pahl & Baeuerle,1995)**.** However, although several studies make a distinction between EOR and UPR, the majority of the literature considers the ER stress-mediated activation of **NF-κB** as UPR-dependent-

considering that in recent years, the comprehensive study of UPR have uncovered several intricate pathways able to manage the resolution of the ER stress, amongst which **NF-κB** activation is considered, as we just have seen. These complex mechanisms not only implicate the ER itself but also other cellular compartments such as mitochondria or the cytoplasm, which are supposed to communicate with each other through a crosstalk between signal transduction pathways (Verfaillie et al., 2012; Xu, W. et al., 2005).

UPR pathways were, at the beginning, only considered to be the IRE1α, PERK and ATF6's response to misfolded proteins, which orchestrates the canonical effector mechanism. In this sense, the UPR had the only purpose of targeting chaperone machinery-related genes. Nevertheless, we have been discussing that UPR has been increasingly defined as a mediator of some other cellular responses such as inflammation or apoptosis. In this context, **NF-κB** activation, as part of the EOR pathway, could be considered to be a non-canonical UPR-dependent and stimuli-specific response. Along these lines, when describing the basis of the rare neurodegenerative disorder FENIB, (Pahl & Baeuerle, 1995) set the term EOR further aside to give rise to the term Ordered Protein Response (OPR), since it was believed to better reflect the nature of the disease. Then, EOR (as well as OPR) could be understood as an individual pathway, while not independent, for the sake of distinguishing a specific effector response inside the much more complex system that UPR has shown to be. Different names would, therefore, be used as a linguistic tool to differentiate specific aspects of the same response.

ER stress, NF-κB and inflammation

According to Schreck et al. (1991) experiments, the later named EOR response, from now on considered as a UPR-dependent NF-κB-mediated response, showed an association with **oxidative stress** (Schreck et al., 1991). Indeed, antioxidant treatment of HeLa cells prevented the expression of NF-κB under ER stress (Pahl & Baeuerle, 1995). Therefore, the origin of the oxidative stress was theorized to be in the environment of the ER, cytochrome p450 from ER membranes, Ca^{2+} release from the organelle, etc. Current understanding of the mechanisms leading to this type of UPR-dependent response will be depicted in this section.

UPR induces oxidative stress

The ER generation of oxidative stress is based on redox reactions held in the lumen. These reactions are part of the protein folding process, which in several cases involves the production of disulfide bonds, an oxidative process (Malhotra & Kaufman, 2007; Tu & Weissman, 2004). Therefore, the ER lumen has an oxidizing environment that maintains its protein folding capacity. The presence of unfolded or misfolded proteins require the collaborative work of several ER resident chaperones, oxidoreductases, and isomerases, along with the activation of other already discussed UPR effector mechanisms, to cope with the created stress. Due to the nature of the reactions that take place in the ER for protein folding, although acute ER stress can be easily dissipated, exacerbated and unresolved stress might promote the production of reactive oxygen species (ROS), nitric oxide (NO) or reactive nitrogen species (RNS) that further worsen the situation, leading to a different effector response: alarm, or apoptosis if ER stress-coping mechanisms are exceeded (Gloire et al., 2006; Gotoh & Mori, 2006; Harding et al., 2003).

Reactive Oxygen Species

ROS are chemically reactive species containing oxygen that can result extremely damaging for the cell. They are produced under several stimuli, from exposure to pollutants, secretion of cytokines to neuromodulation or, in this case, as a consequence of the accumulation of unfolded proteins. The amount of ROS and consequent level of oxidative stress experienced by the cell produce different types of responses, **including inflammatory response through NF-κB** when those levels are mild. In contrast, low levels of oxidative stress will lead to the transactivation of antioxidant enzymes whereas high levels will result in apoptosis through the impairment of mitochondrial permeability transition pore (Gloire et al., 2006).

ROS, as inflammation mediators, are usually generated upon pathogen detection, irritants or cellular damage. In this sense, since ER stress has been shown to converge with inflammatory pathways, it is no surprise that ER-stress coping mechanisms may lead to the production of ROS Zhang, K. & Kaufman, 2008). ROS can be produced through different processes such as the electron transport chain of mitochondria, ionizing radiation or as a by-product of reactions catalyzed by enzymes such as phagocytic and non-phagocytic NADPH oxidases. However, one important source of ROS during ER stress **is disulfide bond formation**, the oxidative reaction usually required for proper folding of proteins (Malhotra & Kaufman, 2007; Tu & Weissman, 2004).

UPR-mediated ROS production

The oxidizing environment of ER lumen is characterized by its high ratio of oxidized glutathione/reduced glutathione (GSSG/GSH). Disulfide bonding is catalyzed by a family of ER oxidoreductases such as **PDI** when cysteine residues within its active site accept two electrons from the substrate protein. The substrate protein is oxidized and, in turn, PDI is reduced. According to studies in yeast, ER-oxidoreductin 1 (Ero1p) oxidizes PDI back and, through a flavin-dependent reaction, electrons are directly passed to molecular oxygen, the terminal electron acceptor. In some cases, **H_2O_2** (obtained from superoxide anion, O_2^- through dismutation reaction) also plays the role of terminal electron acceptor (Ramming & Appenzeller-Herzog, 2012). Depending on the species acting as terminal electron acceptor, the enzymes catalyzing the process are different. In the case of O_2, disulfide bonding is catalyzed by oxidases and in the case of **H_2O_2**, ER resident peroxidases (GPX7, GPX8) (Ramming & Appenzeller-Herzog, 2012, 2013).

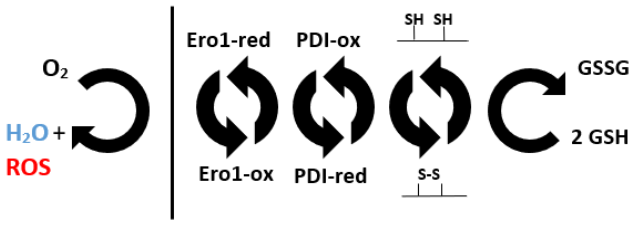

Figure 7. Oxygen is the terminal electron acceptor in the disulfide bonding reactions. Disulfide bonding requires oxidation by PDI, which in turn is reduced. In order to recover its oxidizing capacity, Ero1 reoxidizes it, which in turn is reduced. Reduced Ero1 passes electrons to molecular oxygen, converting it into water. In parallel, non-native disulfide bonding in misfolded proteins must bE reduced prior to refolding.

The reduction of molecular oxygen to water requires the acceptance of four electrons in a kinetically slow process allowing the production of reduced intermediates and by-products (superoxide or hydrogen peroxide) which are highly reactive and damaging to macromolecules. According to (Malhotra & Kaufman, 2007), bacteria couple oxidative folding with the respiratory chain, avoiding this problem thanks to the activity of electron transport proteins. However, in eukaryotes, oxidative

folding occurs in the ER, a different compartment to where electron transport chain is found. Therefore, FAD an oxidant with low redox potential, unlike quinones, helps Ero1p pass electrons to O_2 (Fig.7). The production of **H_2O_2** as a result of the transfer of two electrons to **O_2** appear to be at substoichiometric levels but might be sufficient to cause significant oxidative stress (Harding et al., 2003; Tu & Weissman, 2002; van der Vlies et al., 2003). Therefore, during ER stress conditions, if the amount of misfolded proteins in the ER lumen increases, re-folding becomes prioritized in the organelle, leading to the usage of more oxygen as terminal acceptor of electrons consequently leading to formation of some ROS. On the other hand, ROS production is also suggested to increase as a consequence of GSH depletion achieved through the reductive activity required to be exerted on non-native disulfide bonds of misfolded proteins in order to later refold them (Zhang, K. & Kaufman, 2008) This process requires further interaction of PDI and ERO1p with the newly unfolded protein to correct its structure (Tu & Weissman , 2004). As a consequence, successive cycles of GHS spent, and ROS produced would start. This greater oxidative environment appears to contribute to the accumulation of unfolded proteins due to the inactivation of ER resident proteins (such as PDI) by means of a preferential oxidation of these over the misfolded ones (Verfaillie et al., 2012). All in all, according to (Oyadomari et al., 2001) calculations, ER stress-mediated production of ROS could account for an estimated 25% of the total amounts in the cell.

ROS induction of NF-κB

In the first studies of NF-κB pathway, (Korn et al., 2001) observed that **H_2O_2** was able to induce its activation in a specific way presumably through the degradation of **IkBα**, since other nuclear factors were not activated after treatment with **H_2O_2**. However, this effect is largely dependent on the cell-type and stimulus, exhibiting different mechanisms for NF-κB release (Tu & Weissman, 2004). An example of this specificity is **ROS** inhibition of pro-inflammatory cytokines-mediated NF-κB activation takes place in lung epithelial cells by attenuating IKK complex's activity (Korn et al., 2001; Tu & Weissman, 2004).

Mitochondria-ER crosstalk in the promotion of cellular stress

UPR-mediated ROS production can also be obtained by mitochondria. The link between (1) the formation of ROS in ER due to the impairment in proteostasis and (2) its production in mitochondria, is **Ca^{2+}**. The controlled release of ER stores of calcium Ca^{2+} allows it to work as a secondary messenger in the communication between these two organelles through mitochondria-associated ER membranes (MAMs), fostering great diversity of function such as lipid synthesis, apoptosis, calcium transfer or UPR (Carreras-Sureda et al., 2018; Gotoh et al., 2002; K. Zhang & Kaufman, 2008). Insults such as **depletion of Ca^{2+}** from ER lumen can result in the induction of ER stress triggering UPR and starting complex intercommunication with mitochondria, leading to inflammation and potentially apoptosis. Ca^{2+} is thousands-fold more abundant in the ER lumen than it is in the cytosol, although the vast majority is bound to chaperones (calnexin, calreticulin, BiP, …) (Coe & Michalak, 2009).

ER calcium directs the communication between mitochondria and ER stress

Calcium dynamics during ER stress are governed by different channels and receptors. Normally Ca^{2+} intake happens through SERCA (Sarco-endoplasmic reticulum Ca^{2+} Transport ATPase) an ATP-dependent pump. On the other hand, calcium release takes place through the widely expressed

inositol-1,4,5-triphosphate (IP_3)-receptor (**IP_3R**) or ryanodine receptors (**RyR**), highly expressed in muscle cells and neurons.

During ER stress, ROS produced in the ER lumen as a consequence of disulfide bonding sensitizes IP_3R (Malhotra & Kaufman, 2007), allowing the release of calcium. **Ero1α** is also a positive regulator of IP_3R, enhancing more calcium efflux from the ER (Anelli et al., 2012; Li et al., 2009)

Ca^{2+} travels to mitochondria, which under these circumstances relocate around ER, and increase ATP production in early UPR phases (Bravo et al., 2011). It is then up taken and upon reaching the mitochondrial matrix, Ca^{2+} can accumulate and depolarize the inner membrane (Görlach et al., 2006) opening the mitochondrial permeability transition pore (mPTP) and promoting the release of cytochrome c, which blocks complex III of the electron transport chain. At the level of this complex, the Q cycle takes place and accumulates ubisemiquinone radical intermediate (QH*) when inhibited. The level of this accumulation reflects the levels of ROS released to the cytoplasm, specifically, superoxide and **H_2O_2**, already mentioned to induce NF-κB signaling pathway (St-Pierre et al., 2002). Furthermore, accumulated Ca^{2+} in mitochondria stimulates TCA cycle, consuming O_2 and generating ROS. Besides, opening of mPTP releases GSH, compromising cell's antioxidant capacity (K. Zhang & Kaufman, 2008).

ROS produced in mitochondria can feedback to the ER, further sensitizing IP_3R and allowing the release of more Ca^{2+}. And, since chaperones in the ER lumen (calreticulin, calnexin, BiP, …) depend on Ca^{2+}, ROS-dependent release of calcium contributes to the accumulation of more unfolded proteins, in turn, exacerbating the UPR and closing the cycle.

Ultimately, Ca^{2+} can stimulate the production of reactive nitrogen species (RNS), which is known to inhibit complex V of the mitochondrial electron transport chain promoting further ROS production.

ROS produced in high quantities can lead to apoptosis and therefore, the cell has developed mechanisms to fight this oxidative stress. Among these mechanisms, the branch of PERK in the UPR is activated with objective of avoiding ROS accumulation-induced apoptosis. For instance, ATF4 mRNA is preferentially transcribed which, along with Nrf2 (also activated by PERK) promote the maintenance of glutathione, the main redox buffer in the cell (Malhotra & Kaufman, 2007). This way, PERK alleviates ROS-produced toxic oxidative stress, giving time to the cell to combat the cause of its production (K. Zhang & Kaufman, 2008).

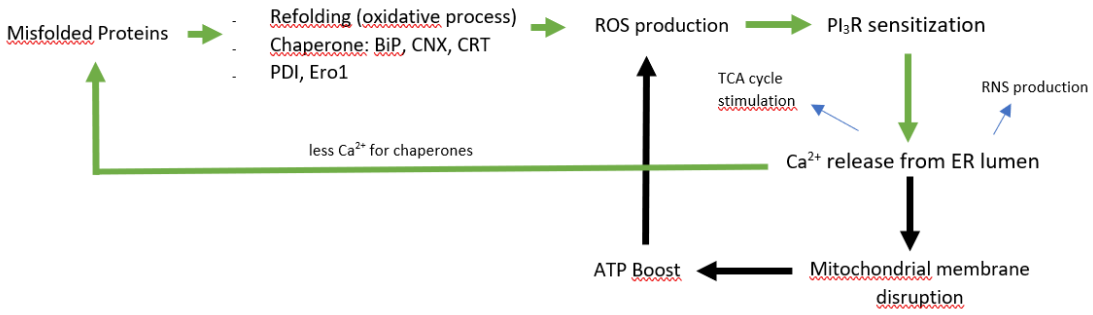

Figure 8. Vicious stress cycle derived from ER stress induced UPR and its crosstalk with mitochondria. Misfolded proteins (or other stimuli triggering ER stress) require folding machinery to revert wrong placement of disulfide bonding. Chaperones are great part of these machineries and are dependent of ER Ca^{2+}. Furthermore, disulfide boding reactions produce ROS as by-product which sensitizes PI_3R channels and promote ER Ca^{2+} efflux, affecting chaperone folding capacity. Mitochondrial membranes are sensitive to Ca^{2+} and disruption is observed, leading to cyt c release but also ATP boost due to the high ATP requirements. This further promotes ROS production. RNS is produced as a response of ER Ca^{2+} depletion.

Nitric Oxide

NO also contributes to the oxidative stress experienced by cells during UPR activation. Nitric oxide (NO) is a multifunctional biomolecule produced from the amino acid L-asparagine by NO synthase (NOS) with the aid of co-factors such as heme, FAD or NADPH (Ignarro, 2000). It is an important intracellular and intercellular signaling molecule. NO is a free oxygen radical and thus, may have cytotoxic effects on cells. An overproduction is implicated in several diseases such as diabetes or autoimmune diseases where NO can lead to an apoptotic cellular fate, mainly observed through the activation of mitochondrial pathways.

There are different types of NOS, constitutive (cNOS) and inducible (iNOS). Endothelial NOS (eNOS) and neuronal NOS (nNOS) are Ca^{2+}- and calmodulin-dependent cNOS and are constantly present in resting cells, only producing low concentrations of NOS by demand. On the other hand, iNOS activation can be induced by **cytokines**, bacterial products, and other immune threats. iNOS are Ca^{2+}- and calmodulin-independent and produce high levels of NO upon activation, mainly used to attack invaders. However, overproduction of NO by iNOS can lead to damaging effects depending on the cell type (Xia et al., 2001). For instance, macrophages can induce iNOS under inflammatory conditions such as those exhibited upon the activation of **NF-κB** pathways, enhancing the progression of diverse inflammatory diseases such as rheumatoid arthritis, diabetes, multiple sclerosis, and other neurodegenerative disorders. Indeed, astrocytes and microglia (brain resident macrophages) produce NO by iNOS as a result of inflammatory processes carried during these pathologies (Bowie & O'neill, 1999; Musial & Eissa, 2001; Pacher et al., 2007).NO interaction with oxygen generates reactive nitrogen oxide intermediates (RNOIs) which further react with thiol or amine residues in biomolecules potentially provoking conformational changes due to the formation of S-nitrosothiols (Gotoh & Mori, 2006).

NO induces UPR activation

NO activates ER stress responses either by inhibition of SERCA-mediated Ca^{2+} influx in the ER, achieved through a tyrosine nitration of the channel-like domain (Pacher et al., 2007); or by increasing RyR1 and Ryr2 Ca^{2+} efflux. Either case trigger ER stress by prohibiting the function of Ca^{2+}-binding chaperones. IRE1, ATF6 and PERK activation have been observed after treatment with NO donors in different cell types (Gloire et al., 2006). Furthermore, NO disrupts complex IV function of the respiratory chain by binding to it and competing with oxygen. Thus, ROS production is promoted (Kröncke et al., 1998; Reichenbach et al., 2001), aggravating Ca^{2+} depletion and inducing the activation of inflammatory pathways (Fig.8.).

Link between NO and **NF-κB**

Regulation of NO by iNOS occurs at various levels, being the transcriptional level the most important. iNOS promoter region has binding sites for **NF-κB**. Therefore, **NF-κB** mediates NO expression Nakagawa & Yuan (2000) and Yoneda et al. (2001). Suppression of **NF-κB** pathway through the degradation of IKKβ also abolishes iNOS induction, while H_2O_2 induction of **NF-κB** promotes iNOS activation(C.-Y. Wang et al., 1998). Consequently, cytokine production achieved through UPR-dependent activation of **NF-κB**, links ER stress to the activation of this transcription factor and the consequent inflammatory process observed during alarming UPR.

Programmed cell death and NFkB

NF-κB is the major regulator of innate immunity responses in several cell types and is the chief mediator of the UPR-derived inflammatory response during the activation of the alarming effector mechanisms. However, as the ER stress progresses and the capacity of the cell is exceeded, pro-apoptotic programs are started, committing the cell to a fatal fate. This is observed under uninterrupted or severe ER stress. Different UPR-dependent transcriptional programs activated upon high levels of ER stress can lead to programmed cell death (PCD). Additionally, although apoptosis is generally the most studied UPR-dependent PCD pathway, necrosis is also considered to be a consequence of this kind of stress since it is classically linked to excessive inflammation (Estornes et al., 2014)

Alarming UPR signaling programs change to programs known as "terminal UPR", leading to mitochondria-dependent and independent apoptotic pathways to eliminate damaged cells (Fig.9.).

Apoptosis is by far, the most extended death-targeting response as a consequence of induced ER stress. It mainly relies in a set of caspase-dependent pathways activated in different ways: ER mediated responses to stress, like caspase 12 pathway, or through mitochondrial-dependent ER signal amplification (Nakagawa et al., 2000). For instance, although activating signals are different for each caspase family, caspase-12 pathways can also be induced by UPR. (Not confirmed in 2006). After Ca^{2+} release from the ER to the cytosol, m-calpain, a Ca^{2+}-dependent cysteine protease, cleaves procaspase-12, activating it(Park et al., 2000; C.-Y. Wang et al., 1998). Cas-pase-12 activates procaspase-9 to activate procaspase-3, the executioner of cell death (Kaufman, 2002) According to (Papa et al., 2004), IRE1/TRAF2 and caspase-7 would also participate in this activation.

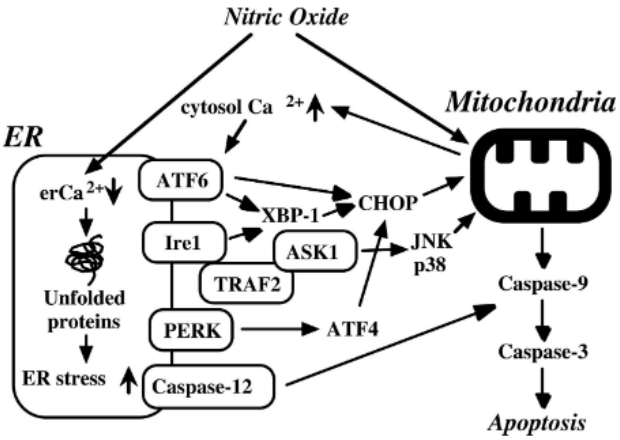

Figure 9. NO, ROS and ER stress trigger apoptotic pathways in cooperation with mitochondria. *Adapted from Kaufman (2002).*

TNFα-induced JNK-mediated apoptosis

UPR can also induce apoptosis in a collaborative manner with mitochondria through the induction of tumor necrosis factor- **α (TNFα) pathway.** Interestingly, **TNFα** is an intensively investigated **NF-κB** target gene because it can feedback to tumor necrosis factor alpha receptor 1 (TNFR1) in an autocrine fashion and further promote inflammation. However, TNFR1 receptor exhibits a dichotomous activity by being able to trigger two opposing pathways: JNK and NF-κB, ultimately modulating cell's fate. JNK pathway activates the death-inducing signaling complex (DISC)-dependent TRADD-FADD-caspase 8 pathway leading to cell death when TRADD recruits FAD and caspase 8 is activated (Hu et al., 2006).

Caspase 8, in turn, induces permeabilization of the mitochondrial outer membrane and the consecutive release of cytochrome c activates the intrinsic apoptotic pathway.

Several authors describe an accumulation of ROS upon **TNFα** binding to TNFR1 as a major contributor to this type of induced cell death. These ROS are proposed to either come from the oxidative burst suffered in mitochondria upon ER stress or from an extra-mitochondrial source. Either way, downstream JNK, ROS induces prolonged JNK activity by oxidizing MAPK phosphatase (MKPs)'s critical cysteine residues to sulfonic acid (Kamata et al., 2005). Hence, MAPKs activity is sustained leading to necrotic or apoptotic cell death through the activation of caspase 8, some studies suggesting that the localization of ROS production, down- or up-stream JNK, may be the responsible for the selected cell death. In addition, **TNFα** pathway can be activated through the direct effect of ROS on ASK1 (Win et al., 2014). Activation of ASK1 is redox-dependent. In unstressed condition, thioredoxin (Trx), a ubiquitously expressed reduction/oxidation (redox)-regulatory protein, binds ASK1, and inhibits its kinase activity. Oxidized Trx cannot bind to ASK1. Therefore, ROS-treated cells avoid ASK1 inhibition by Trx and show sustained **TNFα** activation ((Win et al., 2014)**.**

Altogether, JNK-dependent apoptotic mechanism is not that simple. According to (Hetz, 2012; Ma & Hendershot, 2004), TRADD-FADD is generally inhibited by a TRAF2-cIAP complex, which does not allow the progression of apoptosis signaling even in the presence of apoptotic stimuli (Urra et al., 2016). Therefore, to permit the progression of apoptotic signaling, upon TNFα stimulation, BID is cleaved in a caspase-8 independent manner, generating jBID. jBID later translocates to mitochondria inducing selective release of Smac/DIABLO which goes back to the cytoplasm, disrupting the TRAF2-cIAP complex and allowing for TRADD-FAD-dependent caspase 8 activation (C. Wang & Youle, 2009). On this wise, TNFα-induced JNK-mediated response would have a pivotal role in the promotion of apoptosis (Deng et al., 2004).

JNK is one of the major mitogens activated protein kinase (MAPK) cascades (along with ERK and p38 pathways) which can be counteracted by MAPK phosphatases (MKPs) (Kamata et al., 2005). In this sense, duration, and amplitude of the TNFα-induced JNK cascade is modulated by the equilibrium between inducing kinases and inhibiting phosphatases. Interestingly, accumulated ROS as a consequence of **TNFα** signaling, can feed a loop in JNK activity by interacting with MKPs. This avoids JNK pathway inhibition which, together with ROS-driven oxidation of ASK1, promote sustained activation of JNK leading to apoptosis (Win et al., 2014).

NF-κB regulation of TNFα-induced JNK-mediated apoptosis

In this apoptotic context, NF-κB induced upon IRE1-TRAF2 association and IKK-mediated IκBα degradation, is suggested to modulate the stressed cells outcome. NF-κB appears to apoptosis through the selective transcription of anti-apoptotic genes. Indeed, it was observed that cells deficient for NF-κB activation exhibited higher susceptibility to apoptosis due to an abnormal accumulation of ROS, suggesting that NF-κB displays some kind of protective activity, promoting cell survival (Bubici et al., 2006). This protection is attributed to the activation of anti-apoptotic molecules but also to the attenuation of the TNFα-induced JNK-mediated apoptosis. Attenuation of JNK-mediated programmed cell death is, in part, achieved by interrupting JNK cascade at some point or by diminishing ROS accumulation downstream that pathway. NF-κB does that by transcribing different sets of genes depending on the desired effect. For instance, c-FLIPL, Bcl-2 members or Spi2a block TNFα-induced PCD. The mechanism of said inhibition occurring in early TNFR1 cascade are the prevention of mitochondrial outer membrane permeability (MOMP), events involved in the elimination of cathepsin B in lysosomal-mediated PCD, among others. Also, XIAP, A20 and GADD45β inhibit JNK. For instance,

GADD45β and XIAP directly target MKK7/JNKK2, the most important activator kinase upstream JNK, suppressing the pathway.

On the other hand, FHC (ferritin heavy chain) and MnSOD (mitochondrial enzyme Mn^{++} superoxide dismutase) are also expressed as a result of **NF-κB** signaling (Pham et al., 2004; Sasazuki et al., 2004). Both molecules act synergistically to decrease oxidative stress by sequestering free iron, which is required for ROS production in mitochondria, and promoting dismutation of $*O_2^-$ into H_2O_2. H_2O_2 is later used by peroxidases, diminishing the possibilities of further promoting JNK activation through ASK1.

Normally, TNFα is not a strong death inducer but severe stress appears to induce serious sensitivity to TNFα toxicity (Hu et al., 2006). Decreased levels of TRAF2, observed under ER stress, may be crucial for this process, especially considering its already discussed role in blocking FADD-TRAD-caspase 8 dependent apoptosis.

Subsequent levels of complexity in this regulation are exemplified by the fact the JNK phosphorylates p53, c-Jun and c-Myc, activating them, while also stimulates BIM but represses anti-apoptotic Bcl-2 molecules through phosphorylation (Bogoyevitch & Kobe, 2006). In addition, BH_3-only proteins, such as the previously mentioned BIM, are expected to modulate IP_3R -mediated Ca^{2+} release from the ER lumen (Parys, 2014). Ero1α, as a positive regulator of IP_3R, further contributes to Ca^{2+} depletion (Anelli et al., 2012). Cytosolic Ca^{2+} add to the JNK pathway through Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), augmenting ROS production through NOX2 or NOX4. This, in turn, leads to oxidative stress and a positive feedback regulation of CHOP through PKR. CHOP, in turn, inhibits NF-κB and AP1 (Li et al., 2010).

To sum up, JNK pathway, as well as NF-κB, is highly dependent on cell type, nature and the duration of the stimulus. It is suggested that JNK promotion of apoptosis relies on the accumulation of different effectors such as jBid or Smac/Diablo (Bi et al., 2005; Blais et al., 2006). Also, upon TNFα stimulation, the contribution of JNK is determined by NF-κB-mediated inhibition. TNFα is a potent activator of NF-κB, which in turn is a potent inducer of TNFα, while such events are contemplated under the umbrella of processes triggered by ER stress-induced UPR. It is worth noting, however, that there are other possible origins for these signaling cascades, and it is often difficult to elucidate the correct source, especially in the evaluation of the etiopathogenesis of a disease. Indeed, inflammation is a complex response triggered by a large variety of stimulus, as discussed in this work, from infections to ER stress. Nonetheless, due to its broad presence in a great variety of pathological conditions, the potential implications on major clinical problems and the limited spotlight occupied in the scientific picture until now, UPR-derived NF-κB-mediated inflammation deserves and requires further attention.

Diseases

The observation of NF-κB being one of the chief modulators of UPR-induced inflammation under ER-stress is consistent with the fact that it is one of the major mediators of the inflammation accompanying the pathogenesis of some diseases. The presence of inflammation might be beneficial or detrimental depending on the disease, cell type and other factors. For instance, we can observe this dichotomic function in cancers (Hoesel & Schmid, 2013). Other conditions in which ER-mediated inflammation is present are metabolic diseases such as diabetes, airway diseases such as cystic fibrosis and very importantly, neurodegenerative disorders. A common characteristic among the cells

implicated in these disorders is their dependence on ER pathways due to a high protein synthesis demand or requirement for highly developed secretory pathways such as B cells, β-cells and so on. On the other hand, neurons and glial cells are also susceptible to suffer from exaggerated ER stress due, not only, to their secretory function but because, especially in the case of neurons, they do not conserve the ability of undergoing mitosis. Therefore, ER stress is not diluted during division but accumulated until reaching dangerous levels (Roussel et al., 2013). Altogether, there are several diseases in which UPR activation leads to inflammation which can either stop or enhance its progression. However, only those in which NF-κB plays a major role will be presented in this work.

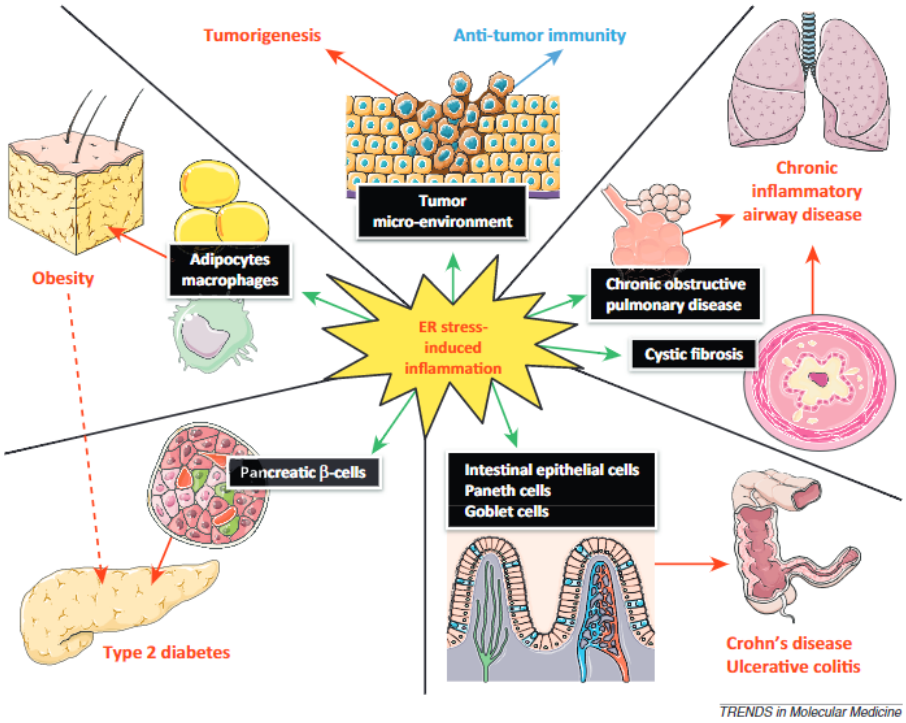

Figure 10. ER stress-induced inflammation is observed in several pathologies including cancer, metabolic diseases, airway diseases, neurodegenerative diseases (not depicted in the figure) and Chron's disease (not described in this work) (Garg et al., 2012).

Cancer

Cancer is a group of several and diverse diseases characterized by uncontrolled growth and multiplication of cells sometimes also acquiring the capacity of invading other parts of the organism. There are more than 200 types of cancers classified by anatomical localization. Thus, it is not possible to talk about "cancer" in a generalized manner, especially taking into account the specificity of effects observed by the mediators herein presented. For this reason, the different studied mechanisms will allude to a specific type of cancer in an attempt to minimize generalization.

Extrinsic and intrinsic factors such as hypoxia or genomic instability, among others; can cause high demand of protein production, promoting the accumulation of misfolded proteins and ER stress induction (Y. Ma & Hendershot, 2004). Indeed, UPR is known to work as an adaptive mechanism during cancer progression by modulating processes that trigger cell transformation or survival (Urra et al., 2016) Recent evidence links UPR activation with the acquisition of many hallmarks of cancer such as metastasis or angiogenesis (Pereira et al., 2010)

PERK deficient cells show the development of smaller tumors and increase animal survival, being implicated in the progression of different types of tumors (Bi et al., 2005; Blais et al., 2006). On the other hand, IRE1α has shown to be involved in breast cancer (X. Chen et al., 2014), pre-B acute lymphoblastic leukemia (Kharabi Masouleh et al., 2014), multiple myeloma, etc. Additionally, IRE1α has been linked to metastatic progression and resistance to chemotherapy (Shajahan et al., 2009). Therefore, different inhibitors of UPR sensors could be beneficial in the treatment of patients carrying these types of cancer.

In cancer, inflammation is found to have a dual function in a cancer-type specific manner. Whether originated from immune infiltrates or cancer cells, inflammation seems to generate an ideal microenvironment for tumorigenesis. However, in certain conditions such as bladder cancer, inflammation is proven to play an anti-tumorigenic role as confirmed by its responsiveness to bacilli Calmette-Guérin (BCG) treatment, a vaccine against tuberculosis also used as immunotherapy due to its immune system enhancing capacity (Vazquez-Lavista et al., 2007).

ER-stress induced inflammation favoring tumorigenesis is observed through pro-inflammatory activity of NF-κB cytokines up-regulation, shown to assist tumor initiation, growth, survival and metastasis (Urra et al., 2016). On the other hand, anti-tumorigenic effects can be caused through NF-κB modulation of immune response against cancerous cells (Sato et al., 2009). Interestingly, both effects might be present at different stages of tumor progression. This dual effect is clearly exemplified in colon cancer with a background of ulcerative colitis, where inflammation drives tumorigenesis while NLR inflammasomeimpedes the development of colon cancer through the induction of piroptosis (Verfaillie et al., 2013).

The variety of cancers linked to constitutive activation of NF-κB is immense, ranging from hematological malignancies such as multiple myeloma, Hodgkin's lymphoma, MALT lymphoma, acute lymphocytic leukemia to solid tumors in breast cancer, lung cancer, gastric cancer, ovarian cancer and many more (Table 1).

Hematological Malignancies	***Solid Tumors***
Multiple myeloma	Breast Cancer
Mantle Cell Lymphoma	Cervical Cancer
MALT lymphoma	Protate Cancer
Diffuse Large B-cell lymphoma	Renal Cancer
Hodgkin's lymphoma	Lung Cancer
Myelodysplasic Syndrome	Pancreatic Cancer
Adult T-cell Leukemia (HTLV-1)	Esophageal Cancer
Acute Lymphocytic Leukemia	Tyroid Cancer
Chronic Lymphocytic Leukemia	Melanoma
Acute Myeloid Leukemia	Bladder Cancer
Chronic Myeloid Leykemia	Cylindroma
	Oral carcinoma
	…

Table 1. Cancers with NF-κB involvement. *Adapted from Bud and Karin, 2009.*

Indeed, mutations in genes coding for NF-κB may have "driver" roles in oncogenesis by either stimulating proliferative pathways or inhibiting apoptosis (Zhang et al., 2017) Moreover, constitutive activation of NF-κB can contribute to chemo- and radiotherapy resistance as observed in multiple myeloma cells (Keats et al., 2007) However, cancers exhibiting a clear relationship between NF-κB and UPR are less in quantity. In this context, the best characterized is breast cancer. Specifically, estrogen (E_2) receptor-positive breast cancer, a common type of breast cancer (approximately 80% of patients). Since, in this condition, cancer cells grow in response to E_2 hormone, it is likely to be treated with anti-hormone therapy. Normally, E_2 synthesis is inhibited or selective E_2 receptor modulators (SERMs, estrogen analogs that impede E_2 signaling through competitive binding to their receptors). Long-term E_2 deprivation, however, requires adaptation through a stress response. In this context, NF-κB is constitutively activated, accounting for growth signals in the cancer cells, acquiring resistance to the anti-hormone therapy. Therefore, a different approach was needed for these patients which later came, paradoxically, from the administration of physiological levels of E_2, leading to apoptosis of cancer cells (Jordan, 2015). Although further study is still required for the complete comprehension of some aspects of the molecular mechanisms leading to the observed E_2-mediated apoptosis, ER stress-derived NF-κB inflammatory processes seems to be the main mediator of this effect. Upon binding to E_2 receptor, E_2 activates some transcription factors with the potential of causing accumulation of unfolded proteins in the ER, consequently inducing UPR. Expression of C/EBPβ (a lipid metabolism-associated transcription factor) is followed, suppressing NF-κB likely through the formation of complexes, avoiding DNA binding of NF-κB. The PI3K/Akt/mTOR pathway, related to cell cycle, is activated due to similarity with C/EBPβ and cell proliferation is promoted. However, later in time, IRE1α and ATF6 activate ERAD, which attenuates PI3K/Akt/mTOR signal and diminishes C/EBPβ's activity, allowing NF-κB- C/EBPβ complex dissociation. In addition, PERK up-regulates the STAT3 transcription factor. Both C/EBPβ's activity attenuation and STAT3 induction promote NF-κB-DNA binding in an IKK-independent pathway. TNF family members are induced by NF-κB, which as already discusses in previous sections, can induce apoptosis. ER stress-induced ROS production, cytokine secretion and intercommunication with mitochondria further enhance the promotion of an inflammatory microenvironment which lead, on balance, to E_2 – promoted programmed cell death. These effects, however, are not observed in one of two main cell types used for laboratory research, demonstrating that these findings might be cell specific and supplementary investigation is required on E_2-mediated apoptosis in breast cancer (Fan et al., 2018)

This case exemplifies the contribution of several diverse factors in either tumor progression or regression such as pro-inflammatory cytokines and ER-produced ROS, respectively (Garg et al., 2012). Furthermore, in cancer, not one but many cells, processes and systems converge. In this fashion, the immune system plays a critical role in almost all the stages of these diseases, either fighting against or promoting their progression. An example of this convergence is the proposed ER stress contribution to the acquisition of tumorigenic environment through its influence on M2 phenotype obtention by macrophages when exposed to media conditioned by cancer cells (Mahadevan et al., 2011). This process, observed *in vitro* and called "**transmissible" ER stress**, activates macrophages by stimuli exerted by surrounding cells, eliciting an inflammatory response in a cell non-autonomous manner adding to the puzzling relationship between UPR, NF-κB and cancer (Urra et al., 2016)

Finally, although it is still controversial due to its pleiotropic physiological role and ubiquitous presence, NF-κB can be potentially targeted with inhibitors in a therapeutic attempt to stop its uncontrolled activation in cancers. This would allow the cells to undergo programmed cell death and chemo- and radiotherapy could be efficient on different tumors that developed resistance.

Central nervous system (CNS)

ER stress has been found to be a hallmark of several neurodegenerative disorders such as Alzheimer's (AD), Parkinson's diseases (PD), multiple sclerosis (MD), Huntington's (HD), amyotrophic lateral sclerosis (ALS), prion related diseases and many more (Roussel et al., 2013). In many of these, accumulation of unfolded or misfolded proteins is observed. The localization of these proteins is not the ER in all the cases, though. In HD, for instance, aggregation of aberrant proteins is found in the cytoplasm and nuclei although UPR is activated either way (Duennwald & Lindquist, 2008). This brings out the complex intercommunication between cell compartments to unify the response against stress. The activation of the unfolded protein response contributes to the characteristic inflammatory process occurring during the progression of these pathologies through the secretion of cytokines, ROS, RNS… (Sprenkle et al., 2017)

In the CNS, NF-κB complexes are expressed by neurons, glial cells (microglia and astrocytes) and oligodendrocytes. NF-κB is critical for synaptic signaling and neuroprotection as well as for brain development. Nevertheless, it was also found to exert opposite functions, playing important roles in neurodegenerative diseases that eventually impair memory or motor function. It is no surprise to observe these contrary activities in NF-κB since it is well known to act in a stimuli and cell-type dependent manner (Tu & Weissman, 2004). For example, in neurons NF-κB is induced by cytokines or other stimuli, promoting the transcription of pro-survival genes like IAPs (inhibitor of apoptosis proteins), Bcl-2, SOD or TRAF1/2. On the other hand, during aberrant inflammatory programs, the activity of NF-κB in glial cells was proven to lead to cell death through the expression of NO in high levels, pro-inflammatory cytokines, and ROS contributing to neuronal dysfunction (Chaudhari et al., 2014). In this sense, sustained neuronal damaged is achieved through the establishment of inflammatory loops (Sprenkle et al., 2017)

Other important processes involved in the clearance of aberrant proteins also seem to be modulated by NF-κB. Autophagy, as the process through which intracellular components undergo lysosome-mediated self-digestion and recycling, appears to play a critical role in neurodegenerative and neuroinflammatory diseases. Its effects, however, are found to be pro- and anti-apoptotic and dependent on stimuli- and cell-type (Liang & Le, 2015). Common regulatory mechanisms for either one or the other autophagy-mediated outcomes have been suggested since both cell death and survival have been concomitantly observed in the same cell. In its pro-survival mode, ER-phagy is used along with ERAD to eradicate the accumulation of misfolded and unfolded proteins.

Autophagy and NF-κB appear to have an interdependence relationship in which autophagy regulates NF-κB and *vice versa*. For instance, studies have shown that TNF-α-mediated activation of NF-κB inhibits autophagy (Ravanan et al., 2017). Anti-apoptotic activity of NF-κB exhibited through the impairment of TNF-α-induced JNK-mediated apoptosis and reduction of ROS production is also illustrated by its repression of autophagy in Ewing sarcoma cells (Djavaheri-Mergny et al., 2006)

Neurodegenerative disorders with great social relevance due to high prevalence will be described in this section.

Alzheimer's Disease (AD)

Alzheimer's disease is a highly prevalent age-related progressive neurodegenerative disorder due to the super aged society we currently live in. AD is also known to be the most common cause of dementia. Patients exhibit gradual decline of cognitive functions and behavioral symptoms such as depression due to impaired synaptic plasticity and terminal neuronal loss. The cause of AD is not

completely understood, and several hypotheses have arisen over time: Aβ cascade, Tau, inflammation, cholinergic and oxidative stress hypothesis, and many more (Du et al., 2018)

AD is characterized by the presence of extracellular amyloid-β (Aβ) plaques (senile plaques), occurring when an improper cleavage of the amyloid precursor protein (APP) is carried out by α-secretase in conjunction with β-secretase. In addition, hyperphosphorylated tau is observed to form intracellular neurofibrillary tangles. Tau protein is a microtubule-associated protein involved in the maintenance of microtubule integrity. In normal conditions phosphorylation-dephosphorylation equilibrium in tau modulate transport through the cytoskeleton (Roussel et al., 2013). Microtubule collapse provoked by hyperphosphorylated tau impede signaling, ultimately leading to apoptosis.

Initially, UPR and AD relationship was discovered as an increase in UPR markers in AD brains. BiP, the most abundant ER chaperone, was found upregulated in neurons from the hippocampus and entorhinal cortex. Similarly, this increase also occurs with HSP72 and HSP73 chaperones (Hamos et al., 1991). Several studies linking AD with ER stress associate the latter chronic activation with cognitive dysfunction and loss of memory observed in the disorder. Phosphorylation of eIF2α appears to be responsible for these effects because memory consolidation is known to require protein translation. Such relationship is supported by studies where inhibition or decrease in PERK, GCN2 and PKR activity resulted in improved cognitive functions (T. Ma et al., 2013) However, global translation attenuation can be achieved through different pathways independent of UPR. Therefore, these results point out that not only ER stress, but other conditions contribute to cognitive impairment in AD. IRE1α also appears to be involved in AD (Sprenkle et al., 2017)

As for the cause of ER stress during AD, aggregation of Aβ is widely suggested to be the connection between both. Several research groups, (Baleriola et al., 2014; Barbero-Camps et al., 2014; Yoon et al., 2012) among others, demonstrated that amyloid-β accumulation can directly induce ER stress. Binding of Aβ to glutamatergic receptors causes the release of Ca^{2+} through RyR and IP_3 receptors, also leading to increased ROS production in mitochondria and caspase-3 dependent apoptosis (Uddin et al., 2020) Additionally, Aβ acts as a ligand for TNFR and TLR4, being able to induce TNFα-dependent signaling pathways (Ledo et al., 2016). On the other hand, ER stress is shown to induce tau pathology and *vice versa* (Ho et al., 2012). In turn, tau pathology induces further ER stress through the proposed mechanisms of impairing ERAD mechanism (Abisambra et al., 2013). Interestingly, although AD is an age-characteristic disease, UPR activation is related to age even in the absence of underlying pathologies (Stutzbach et al., 2014)

Along with Aβ and tau core pathologies, AD patients exhibit chronic brain inflammation (neuroinflammation), mostly attributed to reactive microglial cells (brain resident macrophages) found around senile plaques. Secretion of pro-inflammatory cytokines, iNOS and ROS accompany the inflammatory process. Evidence suggests that microglia have a dual role in the progression of AD. On one side microglia engulfs Aβ aggregates and, on the other, promotes inflammation which, in the long run provokes neurotoxicity and apoptosis. Of note, it is suggested that microglia participate in synaptic pruning during development, but also may promote the progression of AD, depicting its phagocytic function as a double-edged tool.

As already discussed, although it is produced by different stimuli, inflammation can be tightly related to ER stress-induced UPR. Attenuation of global translation can activate NF-κB pathways leading to the expression of several pro-inflammatory cytokines promoting an inflammatory process. Mice models of AD show TNFα expression under systemic inflammation in dependency of aforesaid attenuation (Carret-Rebillat et al., 2015) (Perry, 2001) describe the several aspects of TNFα involvement in AD pathology. The inflammatory component of AD can be thus derived from prolonged and unresolved ER

stress which activates inflammatory pathways such as NF-κB. Oxidative stress exerted by mitochondrial ROS and nitric oxide (NO) further contribute to the inflammatory process and provoke the ER-related cytotoxicity (Uehara et al., 2006). NF-κB targets inducible NOS (iNOS) gene in mice and humans (Aktan, 2004) iNOS-mediated NO production can produce modifications in proteins, which are found in high levels in AD as well as in other neurodegenerative disorders. Cysteine S-nitrosylation is an example of an irreversible modification induced by NO and involved in AD pathology (Nakamura et al., 2013). Interestingly, this modification is a powerful modulator of ER stress since PDI with this modification is inhibited (Nakato et al., 2015).

Neurodegeneration is therefore, potentially derived from unresolved ER stress. PERK's ATF4 selective transcription induces the expression of CHOP, which together with GADD34 or caspase 12 orchestrate the UPR-dependent apoptotic events observed in AD patients (Roussel et al., 2013) In contrast, XBP1s may exert a protective function over neurons. In fact, a polymorphism associated to XBP1s appears to increase the risk of developing AD, although it has been suggested that this protection might come from a hypothetical IRE1α-independent XBP1s function (S.-Y. Liu et al., 2013).

Therefore, if UPR is directly or indirectly involved through the promotion of inflammatory processes in the development of AD, therapeutic approaches targeting these mechanisms might help to halt the progression of the disease. Several fronts are open. In terms of antibodies targeting pro-inflammatory cytokines able to induce and induced by NF-κB pathway: Canakinumab (anti-IL1β), Infliximab (anti-TNFα) (Lourenco et al., 2013), Etanercept (TNFα inhibitor) (Butchart et al., 2015).

Other compounds, such as Anakinra, an IL-2 receptor antagonist or Minocyline, have been proposed as interesting candidates to treat NF-κB derived inflammation. Interestingly, minocycline, an antibiotic with anti-inflammatory properties was suggested to modulate reactive microglia in AD helping the system to recover normal phagocytic activity to eliminate Aβ aggregates but also alleviate excessive expression of phosphorylated eIF2α as shown in AD mice models. Minocycline in Alzheimer's Disease Eficacy (MADE) trial was originated to address these proposed properties in patients suffering from mild AD. However, recently published results concluded that treating mild AD with minocycline resulted in any clinically meaningful difference in the rate of cognitive and functional ability deterioration (Howard et al., 2020) This resulted in similar outcomes in trials assessing minocycline effects over other neurodegenerative disorders such as ALS, in which minocycline worsened the disorder (Gordon et al., 2007), or Huntington's disease where it had no effect (Cudkowicz, 2010). These results rise questions about the level of implication of inflammation in neurodegeneration and suggest inflammation to be a merely reaction to pathologic characteristics of the disease. On the other hand, the positive results in models may suggest that toxicity limitations in humans may be the reason of the lack of efficacy of minocycline and not that inflammation is not an important factor in neurodegeneration. Neither anakinra or canakinumab have been tested for AD yet.

Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune chronic inflammatory disease of the CNS. It is characterized by a variety of symptoms amongst which changes in vision, tremors, cognitive deficiency, or muscle weakness are included. At the molecular level, these symptoms are provoked by demyelination of axons, leading to axonal loss and the consequent neurodegeneration over time. This phenotype is caused by the attack of autoreactive T cells from outside the CNS which have been able to surpass the protection of blood-brain barrier (Hussman et al., 2016). The secretion of pro-inflammatory cytokines by reactive immune cells stimulates microglia and astrocytes and further recruits more inflammatory cells which end up inducing plasma cell production of antibodies (Abs) against myelin sheath (Archelos

et al., 2000). The inflammatory process carried out during the disease affects synaptic communication ultimately leading to loss of cognitive, motor, and sensory capacity.

The ultimate cause is unknown but environmental and genetic factors appear to contribute in different levels to the development of the pathology. For instance, vitamin D deficiency may play a not yet completely understood role in the onset of MS, while 20% of the cases have shown an underlying inheritable genetic susceptibility (Gourraud et al., 2012). Also, autoreactive T and B cells might be explained by the similarity between some viral antigens presented by MHC II and myelin components. The Epstein Barr Virus and the Human Herpes Virus 6 are viruses with this characteristic (Sprenkle et al., 2017).

Several studies have shown the implication of UPR in this pathology through the observation of ER stress markers in MS patients and experimental autoimmune encephalomyelitis (EAE), the mice model for MS (Stone & Lin, 2015). Increased levels of ER stress molecules have been found in post-mortem tissue of MS patients (Cunnea et al., 2011). Also, although eIF2α phosphorylation has been found to exhibit a protective effect on myelinated neurons, in MS this process may be impaired leading to ambiguous effects (Roussel et al., 2013)

Interestingly, (Stone & Lin, 2015)suggest that the initial UPR induction in MS pathology may derive from inflammation and not the other way around since inflammatory mediators such as cytokines, ROS and RNS can provoke ER stress. However, as already discussed, both processes feedback into each other, so once UPR is induced, inflammation will be further promoted if the stress is not mitigated. In this sense, PERK activation in oligodendrocytes is found to induce NF-κB *in vitro* and *in vivo* (Lin et al., 2012). It is worth noting that, in MS and EAE, NF-κB has a dichotomous role. On the one hand, its activation in inflammatory cells promotes disease progression, while on the other hand, in neurons and oligodendrocytes it exerts a protective function (Stone et al., 2017). Due to the ambiguous relationship between NF-κB and MS, NF-κB κB appears to be a poor target for treatment (Yue et al., 2018).

Furthermore, as for NF-κB roles in MS pathology, it is associated to autophagy regulation, which is found to be constitutively active in this disorder contributing to disease progression (Andhavarapu et al., 2019). Also, A20, a ubiquitin-editing enzyme, is up-regulated by NF-κB and controls its activity through negative feedback (Afonina et al., 2017). MS patients show decreased A20 levels in whole blood and peripheral blood mononuclear cells as compared to healthy controls. Dysfunctional A20 is proven to lead to exacerbated systemic inflammation and autoimmunity in human and mice models. These effects are consistent with mentioned NF-κB consequences in inflammatory cells, potentially accounting for important aspects of the MS ethiopathogenesis. Indeed, other NF-κB inhibitors might show similar decreased levels in MS, which is further supported by the observation of decreased levels of the inhibitor Nurr1 (nuclear receptor related-1 protein) in MS. Said reduction is also noticed in Parkinson's disease (Perga et al., 2017).

Parkinson's Disease (PD)

Parkinson's disease is caused by the loss of dopaminergic neurons in nigrostriatal pathway over time. It provokes dyskinesia, tremor and rigidity. A hallmark of PD is the presence of inclusion bodies called Lewy bodies, aggregated α-synuclein (α-syn) being their main constituent. Mentioned aggregates produce neuronal dysfunction and degeneration, leading to motor deficits. In physiological conditions, α-syn are found in synaptic sites regulating neurotransmission. In α-synucleinopathies, α-syn accumulates in the ER (Colla et al., 2012). Indeed, sporadic PD brains show raised PERK levels

(Hoozemans et al., 2007) A variety of drugs that cause parkinsonism such as 6-OHDA or 1-methyl-4-phenylpyridinium (MPTP), extensively used in the study of the disease, are shown to promote ER stress (referencia). Evidence explaining α-syn aggregation-derived pathogenesis include the observation of mitochondria-associated endoplasmic reticulum (ER) membranes (MAMs)-bound α-syn. When MAMs lack α-syn, mitochondrial lipid composition, function and trafficking is disrupted (Ellis et al., 2005)

Moreover, early data showed the relationship between NF-κB and PD as a 70-fold expression of the factor relative to control brains (Hunot et al., 1997). Recently, in a very thorough review, (Bellucci et al., 2020) collected and displayed evidence suggesting a link between α-synuclein pathology and NF-κB dysregulation in PD. It is exposed that NF-κB exerts modulatory effects on the CNS and is involved in several processes as a chief mediator: from aging, protein clearance through autophagy, neuroprotection or immunity. Interestingly, different NF-κB components are observed to exert opposite effects on dopaminergic neurons. While c-Rel appears to provide neuroprotection to neurons and glial cells and its deficiency leads to a PD-like phenotype in mice; Rel A is found overexpressed in PD patients participating in the neurodegenerative mechanisms (Hunot et al., 1997). Furthermore, α-syn can induce nuclear translocation of RelA in microglia while c-Rel expression is decreased in PD patients (Wang et al., 2020). In this sense, c-Rel deficiency or alterations are proposed to increase PD susceptibility. Mitochondrial dysfunction due to high energy demanding dopaminergic neurons with altered c-Rel function can produce high amounts of ROS. This, in the absence of c-Rel might promote exacerbated and vicious inflammatory cycles involving promotion of further ER stress, which would explain protein aggregation, leading to neurodegeneration and disease progression.

Finally, in European and Japanese early onset PD is characterized by the involvement of the *PARK2* gene, which encodes parkin, a ubiquitin ligase. *PARK2* mutations causing PD, impair Parkin activity (Hideki Shimura et al., 2000). In healthy individuals, parkin has the role of targeting damaged mitochondria to autophagy (Narendra et al., 2008). (Bouman et al., 2011) showed that Parkin is up regulated by UPR-induced activation of ATF4 as a response to ER and mitochondrial stress, conferring a cytoprotective effect. Loss of parkin increases cells susceptibility to ER stress. As a result, α-syn can accumulate in parkin deficient brains since, in normal cells, parkin appears to target ER lumenal α-synuclein for degradation (H. Shimura, 2001). This accumulation can induce ER stress triggering UPR as observed in mice models of PD (Colla et al., 2012) which ultimately would induce an inflammatory process under unresolved stress.

Due to its involvement in PD's inflammation and consequent neurotoxicity, NF-κB was proposed as a potential target for therapy (Flood et al., 2011) although similarly to others, anti-inflammatory drugs tested targeting NF-κB have not showed favorable results as shown by a recent meta-analysis on nonsteroidal anti-inflammatory drugs (NSAIDs)' effect on risk of PD (Poly et al., 2019)

Other neurodegenerative disorders that similarly to AD, MS and PD provoke a UPR are Huntington's disease (HD) and Amyotrophic Lateral Sclerosis (ALS). Interestingly, in HD accumulation of proteins does not take part within the ER but in the cytoplasm and nuclei. However, HD also induces UPR responses which might also be responsible for neurodegeneration through ASK1-mediated apoptosis (Jiang et al., 2016). This leads to the proposal of diverse UPR mediators as therapeutic targets. Both diseases are marked by significant neuroinflammation. Also, several studies have evidenced the relationship between these disorders and NF-κB (Mattson & Camandola, 2001; MIGHELI et al., 1997; Napolitano et al., 2008). Last but not least, FENIB (familial encephalopathy with neuroserpin inclusion bodies) is a rare genetic condition characterized by myoclonic epilepsy, frontotemporal dementia, or memory loss. At the molecular level it is caused by mutation is the *SERPINI1* gene, which encodes for a

neuroserpin. The different alterations suffered by the protein due to the genetic insults disable the protein for its proper function and make them susceptible to aggregation in Collin bodies within the ER of neurons and provoking ER stress. The UPR is initiated in the form of NF-κB activation as a response of Ca^{2+} leakage from the ER lumen. Research groups investigating this disease refer to this response as Organized Protein Response of OPR as a modification of the ER-Overload Response (EOR) early proposed by (Pahl & Baeuerle, 1995). However, the mechanisms by which the aggregates exert a toxic effect on neurons are not fully understood.

Metabolic diseases

Metabolic diseases such as diabetes were one of the first diseases to be related to the described relationship between UPR and NF-κB. For that reason, it has been extensively and systematically reviewed generating an immense amount of literature on the topic. Therefore, it must be included in the present work although only selected data will be presented.

Obesity is shown to involve chronic inflammation in metabolic tissues which leads to the inhibition of the insulin receptor (Hotamisligil, 2010). Obese mice show pro-inflammatory cytokine (IL-1, IL-1β, TNF, …) secretion by macrophages and adipocytes. These cytokines have the ability of further inducing JNK and NF-κB pathways which contribute to the progression of the observed inflammatory process, leading to diabetes with increased probability. Indeed, JNK deficient mice appear to be resistant to type 2 diabetes while hepatocytes with IKKβ constitutive expression lead to the development of hyperglycemia and insulin resistance (Vallerie et al., 2008). Interestingly, the three branches of the UPR (IRE1α, PERK and ATF6) are involved in the modulation of glucose metabolism and cellular lipogenesis (Hotamisligil, 2010). Along these lines, Ozcan (2004) proved that obesity can cause ER stress through JNK pathway hyperactivation. However, XBP1 deficient mice develop mild diabetic phenotype, suggesting a protective role.

UPR-mediated autophagy, modulated by NF-κB, and apoptosis have also been reported in the progression of diabetes and other metabolic diseases (Pandey et al., 2019). In pancreas, β-cell apoptosis is triggered by UPR through Ca^{2+} homeostasis disruption upon to exposure to cytokines. Several evidences show a link between UPR and both (1) NF-κB inflammatory pathway and (2) apoptosis achieved through its communication with mitochondria, as already described in previous sections of this work. A deeper understanding of this issue can be achieved through a comprehensive reading of reviews such as Liu, C.P. (2011) and Pandey et al. (2019).

Clinical trials targeting IL-1, a potent NF-κB inducer, with canakinumab and anakinra resulted beneficial as single-drug therapy for new-onset type 1 diabetes. Neither of them prevented β-cell increasing dysfunction. However, mice models suggest that the effect in combination with other immunomodulatory drugs might yield better results (Moran et al., 2013).

Cystic fibrosis (CF)

Cystic fibrosis is a disease that involves the impairment of ion channels. It has an autosomic recessive inheritance pattern and is clinically expressed in multiple forms. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that encodes for a Cl^- transporter, resulting in the accumulation of viscous bronchial and pancreatic secretions which may lead to bronchi plugging and consequent effects. An exaggerated activation of NF-κB has been linked to CFTR

dysfunction, although other inflammatory pathways are also activated (JNK, p38, and AP-1) (Bodas M, 2010).

The most frequent mutation carried by approximately 70% of patients is a phenylalanine deletion in codon 508 (ΔF508), affecting the protein folding and producing a class II cystic fibrosis. This type of CF induces increased transcription on BiP and XBP1 splicing suggesting the involvement of ER stress and UPR which could explain the inflammatory process started later. However, it is worth to highlight the chronic colonization of airways in CF patients by opportunistic pathogens such as *P.aeruginosa, H. influenza* or *S.aureus.* Some of these pathogens are able to promote XBP1 splicing through TLR pathways, suggesting an alternative cause for the induction of NF-κB and other inflammatory pathways. Nevertheless, as pointed out above, there is, to some extent, a relationship between these receptors and ER-stress responses (G. Chen et al., 2019). TLR signaling pathways can be regulated by the UPR through the modulation of secreted pro- and anti-inflammatory cytokine production (Kim et al., 2018) opening the door to a possible more complex crosstalk between UPR, inflammation and infection in CF pathogenesis. All in all, pathogens together with UPR-derived inflammation could promote epithelial damage, induce fibrosis and the consequent pulmonary failure.

All things considered, several diseases, some of them discussed above, share the common characteristic of being proteinopathies or exhibit proteostasis abnormalities. Therefore, it is logical to measure distinct levels of ER stress during their progression. Inflammation is also often observed accompanying these disorders. However, although it is clear that distinct pathways relate UPR and inflammatory processes, especially those derived from the activation of NF-κB, in most cases, whether that inflammation is triggered as a result of ER stress, in the context of each disease, remains unclear. In fact, the proposal of NF-κB as a major contributor to the etiopathogenesis of these conditions led to the study of NF-κB's inhibitors as potential anti-inflammatory treatments. However, as already pointed out in some reviews, targeting ER stress-induced inflammation is not an easy task. First, its mediators exert opposite functions in dependence of different factors, so targeting inflammation can trigger undesired responses in a cell-specific manner. Also, both effects could be mediated by the context of the stimulus even in the same environment. Thus, in order to target inflammation, its beneficial effects must be taken into account. Moreover, since inflammatory and apoptotic pathways intersect at some points in UPR-dependent mechanisms, targeting inflammation alone, might be risky. In order to clarify these issues, several studies addressing this particular crosstalk in specific disorders must be carried out. This might lead to the need of personalized treatments for thoroughly studied cases in order to avoid undesired secondary effects.

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