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TÍTULO PROYECTO : REGULATION OF AN AD-LIKE PROCESS BY THE UPR TRANSCRIPTION FACTOR XBP1 IN VIVO

DISCIPLINA PRINCIPAL : G1 NEUROLOGIA Y NEUROCIRUGIA
GRUPO DE ESTUDIO : MEDICINA G1
INVESTIGADOR(A) RESPONSABLE : CLAUDIA ANDREA DURAN ANIOTZ
DIRECCIÓN :
COMUNA :
CIUDAD : Santiago
REGION : METROPOLITANA

FONDO NACIONAL DE DESARROLLO CIENTIFICO Y TECNOLOGICO (FONDECYT)
Moneda 1375, Santiago de Chile - casilla 297-V, Santiago 21
Teléfono: 2435 4350 FAX 2365 4435
Email: informes.fondecyt@conicyt.cl
### OBJETIVOS

Cumplimiento de los Objetivos planteados en la etapa final, o pendientes de cumplir. Recuerde que en esta sección debe referirse a objetivos desarrollados, **NO** listar actividades desarrolladas.

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<td>1</td>
<td>Specific Aim 1. Evaluate the effects of XBP1 expression on the Abeta seeding process in an animal model of Alzheimer’s disease.</td>
<td>TOTAL</td>
<td>In this aim, we studied whether the presence of ER stress response factor XBP1s reduces Abeta aggregation and prevents AD pathology in transgenic mouse model of AD by evaluating Abeta aggregation using both biochemical and histological techniques. With this specific aim we monitored the impact of XBP1s in several fundamental features of AD in vivo using a robust mouse model of the disease. We evaluated the Abeta load using ThS staining (see results section). As a preliminary result, we observed that animals TgXBP1s/5xFAD showed lower aggregation in hippocampus compared with 5xFAD animals measured by histological and biochemical analysis against Abeta.</td>
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<td>2</td>
<td>Specific Aim 2. Assess the effects of XBP1 on the cognitive impairment observed in Alzheimer’s disease mouse models.</td>
<td>TOTAL</td>
<td>For this goal, we evaluated the potential improvement in learning and memory of an AD transgenic mouse model expressing XBP1s in the central nervous system using different behavioral testing approaches. Here we provide evidence supporting a novel function of XBP1 in enhancing learning and memory-related pathways in wild-type animals. Moreover, our preliminary data using viral vectors to deliver active XBP1 in AD animals also indicates that cognitive capacity can be also restored in the context of this neuropathological condition. Additionally, in order to determine the role of XBP1 in the cognitive development in TgXBP1s/5xFAD mice we will also evaluated in our experimental animals the Morris Water maze behavioral test.</td>
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<td>3</td>
<td>Specific Aim 3. Analyze the impact of XBP1 in the expression of a cluster of Alzheimer’s disease-related genes.</td>
<td>TOTAL</td>
<td>This specific aim involved the evaluation of the expression profile of genes related to APP processing and Abeta accumulation in animals with manipulated XBP1 levels. These genes were previously identified as XBP1 targets in cell culture experiments. Here, we also analysed and intended to obtain mechanistic insights of XBP1 on APP maturation and processing to complement the in vivo analysis.</td>
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Otro(s) aspecto(s) que Ud. considere importante(s) en la evaluación del cumplimiento de objetivos planteados en la propuesta original o en las modificaciones autorizadas por los Consejos.
**RESULTS OBTAINED:**

**Main Goal:** To investigate the role of the Unfolded Protein Response (UPR) transcription factor XBP1 in the development of Alzheimer's disease. In the long term, we also intend to define the possible therapeutic benefits of alleviating stress on the ER using pharmacological approaches in a disease context.

**Hypothesis:** Targeting XBP1 improves memory deficits and decreases amyloid load in Alzheimer's disease models.

**Specific Aim 1. Evaluate the effects of XBP1 expression on the Abeta seeding process in an animal model of Alzheimer’s disease.** In this aim, we studied whether the presence of ER stress response factor XBP1s reduces Abeta aggregation and prevents AD pathology in transgenic mouse model of AD by evaluating Abeta aggregation using both biochemical and histological techniques.

SA1.1. Breeding XBP1s transgenic mice with an AD mouse model.

As proposed in this grant, we were able to generate in house an XBP1s transgenic mouse model that specifically express the active XBP1s form in the nervous system under the control of the PrP promoter (Tg<sup>XBP1s</sup>) (Figure 1A). These animals were backcrossed into C57BL/6 mice for more than 8 generations. Then we have breed these Tg<sup>XBP1s</sup> transgenic animals with a transgenic AD mouse model termed 5xFAD on a pure C57BL/6 genetic background and demonstrated that we were able to generate triple transgenic mice (see examples of genotype analysis of all groups in Figure 1B). 5xFAD overexpress both mutant human APP with the Swedish, Florida, and London Familial Alzheimer's Disease (FAD) mutations and human PS1 harboring two FAD mutations. These mice start to develop amyloid beta (Abeta) aggregates at 2 month old and also show extensive presence of senile plaques, neuronal loss, synaptic degeneration inflammation, and cognitive impairment starting at 4-5 months old. Here, we were able to obtain several litters of Tg<sup>XBP1s</sup>/5xFAD animals to calculate the mendelian rate of birth and observed the expected ration (not shown), indicating no developmental effects of the combination of all transgenes.

At least a total of ten animals per experimental group were generated using our breeding strategy including 5xFAD, Tg<sup>XBP1s</sup> bred with 5xFAD (Tg<sup>XBP1s</sup>/5xFAD), non-transgenic mice, and Tg<sup>XBP1s</sup> animals. All comparisons were performed with the full litters to have appropriate controls. Mice were sacrificed by CO<sub>2</sub> inhalation and brain and blood samples were collected on a routine basis. Half of the brain was snap-frozen at -80°C for future biochemical analyses, whereas the other half was stored for histological studies. In addition, in order to have an appropriate time-course of Abeta deposition, before starting our study we characterized in our hands the development of AD features in experimental groups at different times (3 and 6 months old) by using thioflavin S staining. Because its extensive Abeta accumulation and possible behavioral impartment, we decided to use animals at 6 months old or older.

SA1.2. Upregulation of XBP1s in the nervous system reduces amyloid beta load in AD mice.

In order to evaluate AD features in our animal model, we investigated the levels of amyloid deposition after the breeding with the XBP1s transgenic mouse using Thioflavin S (ThS) staining to visualize amyloid plaques or amyloid deposits. Briefly, brains were processed for histological and quantification analysis. 25-μm-thick serial slices from all
animal groups (10 sections/stain/animal) were analyzed to quantify fibrillar amyloid beta (Abeta) aggregates. Slices were incubated in 0.025% ThS 50% alcohol solution. Image quantification analysis (reactive burden) was performed using the ImagePro software. As shown in Figure 2, we observed extensive accumulation of amyloid reactive deposits in the cortical and hippocampal areas at 6 months old (Figure 2) in both 5xFAD and Tg<sup>XBP1s</sup>/5xFAD transgenic animals. To evaluate the fibrillar amyloid deposits amount in the brain of transgenic animals, we performed extensive quantifications of ThS burden in both cortical and hippocampal areas (Figure 2A and 2B, left panel), including the corpus callosum and the subiculum. However, after the quantification we did not observe differential aggregation profile of Abeta measured by ThS in both cortex and hippocampus of experimental animals, suggesting that XBP1s overexpression does not affects fibrillar Abeta in 5xFAD models at 6 months old.

In order to analyze in detail manner amyloid deposition, the extent of Abeta deposition was then directly analyzed by IHC by comparing all control and experimental groups at 6 month old animals since at this time point the amount of Abeta detected in the model was more robust and reproducible. Briefly, mice were sacrificed by CO2 inhalation and brains were collected. Primary antibody 4G8 was incubated over night at a 1:1000 dilution. HRP-linked secondary goat anti-mouse antibody at a 1:1000 dilution was incubated for 2 h at RT. Peroxidase reaction was visualized using DAB Kit. Finally, sections were dehydrated in ascendant ethanol, cleared in xylene, and coverslipped with DPX mounting medium. Interesting, when we evaluated Abeta deposits in the brain tissue of our experimental animals using 4G8 staining, we observed qualitative differences in cortical (Figure 3A), hippocampal (Figure 3C) and subiculum areas (Figure 3E). Then, we quantified the number of deposits per unit of area and the area of the brain occupied by Abeta deposits reactive against the 4G8 antibody in cortex (Figure 3B), hippocampus (Figure 4D) and subiculum (Figure 4F). Consistent with our hypothesis, we found a lower amount of Abeta deposits in 5xFAD animals bred with our XBP1s transgenic animals compared to 5xFAD, suggesting an important role of XBP1 in Abeta aggregation and the therapeutic potential of delivering of this transcription factor in AD model to test new and validate new treatments.

SA1.3. Biochemical analysis of Tg<sup>XBP1s</sup>/5xFAD transgenic animals.

Abeta soluble oligomers are proposed as relevant neurotoxic species mediating synaptic dysfunction in Alzheimer’s disease. In that sense, we then decided to perform a biochemical analysis to measure the physicochemical properties of Abeta in the brain of our experimental groups. To evaluate Abeta oligomerization, we analyzed the solubility of Abeta in the brain as a measure of its aggregation state and quantified cerebral levels of Abeta<sub>42</sub> in cortical and hippocampal homogenates after a serial extraction protocol with different reagent and ultracentrifugation followed by quantification with a specific human ELISA assay (Figure 4A). Briefly, dissected brain was separated in cortical and hippocampal areas to generate the brain homogenates. To measure Abeta<sub>42</sub> levels the BH were processed using a previously described serial extraction protocol. 10% BH (cortex and hippocampus) were centrifuged in L100K ultracentrifuge tubes (Beckman-Coulter, Brea, CA) at 32600 r.p.m for 1 h at 4°C in a 42.2 Ti rotor. Supernatants were collected and pellets resuspended in 70% Formic Acid (Fisher Scientific, Waltham, MA). Then, samples were centrifuged for 30 min and supernatants were collected. Formic acid fractions were diluted on 1 M Tris Buffer pH 11 (Sigma-Aldrich, St. Louis, MO) 20 folds to neutralize the samples. ELISA was used to measure the levels of Abeta<sub>42</sub> in brain (kit KHB3442, Invitrogen, Carlsbad, CA) following manufacturers advises. This aim was done in collaboration of Dr. Claudio Soto at Houston, where we performed a short research visit to directly perform these experiments. In agreement with our previous results,
Tg\textsuperscript{XBP1s}/5xFAD transgenic animals showed lower levels of fibrillar (formic acid insoluble) Abeta\textsubscript{42} species when compared to 5xFAD control AD mice in cortical (Figure 4D) and hippocampal areas (Figure 4E). Additionally, we evaluated the amount of different Abeta species in cortical area of experimental animals by western blot analysis using 6E10 antibody specific for APP (Figure 5). Briefly, homogenates were sonicated and proteins were quantified as previously described. Protein levels were analyzed by western blot on 10% SDS-polyacrilamide gels. Gels were blotted for APP and Aβ using 6E10 antibody. HSP90 was monitored as loading control. Hippocampal tissue was not analyzed since all material was used for the fractionation experiment. Interesting, we observed that cortical amount of Abeta large aggregates in Tg\textsuperscript{XBP1s}/5xFAD transgenic animals have a reduced oligomeric Abeta species when compared to control 5xFAD (Figure 5C), corroborating the role of XBP1 in APP processing.

Specific Aim 2. Assess the effects of XBP1 on the cognitive impairment observed in Alzheimer’s disease mouse models. For this goal, we evaluated the potential improvement in learning and memory of an AD transgenic mouse model expressing XBP1s in the central nervous system using different behavioral testing approaches.

SA2.1. XBP1s expression enhances learning and memory processes.
To test whether increasing active XBP1s in the CNS improves the learning and memory capacity of mice, we performed several assays to measure the impact of XBP1 in the physiology of the nervous system. Remarkably, the sustained expression of XBP1s in neurons improved the performance in the water maze/memory flexibility assay, where these animals needed less trial to reach the learning criteria (Figure 6A). Consistent with these results, hippocampal slices derived from Tg\textsuperscript{XBP1s} mice showed more sustained and higher amplitude of LTP induced by theta-burst stimulation (Figure 6B). To tease apart possible side effects of neuronal XBP1s overexpression during development and directly investigate its function in the hippocampus, we performed bilateral stereotaxic injections of AAVs to deliver XBP1s (AAV/XBP1s) or a control vector (AAV/MOCK) into the CA1 hippocampal region of adult wild-type mice (Figure 6C). We have previously characterized these AAV constructs in the context of other diseases. Two weeks after AAV injection, mice were tested in the memory flexibility test. Remarkably, local expression of XBP1s in the hippocampus resulted in improved performance in this cognitive task (Figure 7D). These results uncovered an unexpected role of XBP1 in learning and memory, revealing for the first time a physiological role of the UPR in the nervous system.

SA2.2. Therapeutic effects of gene strategy using an AAV/XBP1s based gene therapy in AD mice.
In order to evaluate the possible beneficial effects of XBP1s overexpression over the memory impairment observed in 5xFAD animals, we directly injected 1 month old 5xFAD and WT animals with AAV/XBP1s and control viruses into hippocampus. 5 months (6 months-old) after injection, we study the behavioral performance using the Morris water maze behavioral test (MWM) (Figure 7). Briefly, in this assessment, animals are taught to swim to a hidden platform under the water. At 6 month old, all experimental mice were placed in the pool and allowed to explore it for 1 min. This training procedure was performed six times a day for four consecutive days per animal. On day five, the platform was removed from the pool to measure the time that the animals spend in the target quadrant until the platform was found by the animal. Additionally, during the training phase, the time spent finding the platform was also measured for each animal. As predicted, 5xFAD animals tendency to show memory impairment compare WT mice in all parameters measured in the MWM (Figure 7). Interestingly, we observed that AAV/XBP1s
injected 5xFAD animals improved the learning and memory capability compared with 5xFAD animals injected with control virus, measured by occupancy plot of the animal's group (Figure 8A), latency to the first entry to the platform zone (Figure 8B and 8C), and number of entries to the platform zone (Figure 8D). Thus, enforcement of XBP1s expression locally in the hippocampus may impact two fundamental aspects of AD: (i) it reduces Abeta deposition and (ii) improve higher cognitive functions of the brain involved in learning and memory-related processes. Due to low number of animals in one of our experimental group (n=3), we did not perform statistical data analysis. Now, we are increasing the experimental number of animals.

SA2.3. Morris Water Maze in Tg\(^{XBP1s}\)/5xFAD.

In addition, in order to evaluate behavioral impairment in our AD transgenic animals overexpressing XBP1s, we performed the MWM behavioral test previously described. Although this assay has been shown before to display alterations in the 5xFAD model, we were not able to reproduce these results, obtaining highly variable measurements (Figure 8). We used the Tg\(^{XBP1s}\)/5xFAD animals and the appropriate controls to evaluate cognitive impairment at 6 months of age. Despite of all animals learn how to predict the adverse stimuli (Figure 8A), we were not able to observe significant differences in the experimental groups at the time point analyzed (Figure 8B). However, we are currently performing the test in our experimental groups at 8 months old.

**Specific Aim 3. Analyze the impact of XBP1 in the expression of a cluster of Alzheimer’s disease-related genes.** This specific aim involved the evaluation of the expression profile of genes related to APP processing and Abeta accumulation in animals with manipulated XBP1 levels. These genes were previously identified as XBP1 targets in cell culture experiments.

SA3.1. Expression analysis of AD-related genes in the hippocampus of Tg\(^{XBP1s}\) animals.

An interesting study from Acostar-Alvear et al. determined using CHIP-on-CHIP assays that XBP1s controls a cluster of AD-rerated genes (Figure 9A). These genes are involved in APP trafficking, maturation, quality control and processing. However, in that study only non-neuronal cell cultures were analyzed and until now it is not known if XBP1s control the expression of these genes in the brain in vivo. Based on this report, we developed real-time PCR primers for all the identified genes associated with AD to measure their expression levels in the hippocampus of Tg\(^{XBP1s}\) animals at basal levels. We prepared total cDNA from dissected hippocampal tissue. We were able to show for the first time that a subgroup of these candidate genes is controlled by XBP1s in the brain in vivo (Figure 9B), observing a significant increase of component of gamma-secretase components, CDK5, and Cdk5rap3 at resting conditions in Tg\(^{XBP1s}\) animals compared with litter mate control non-transgenic animals. We are currently analyzing the expression of these genes in Tg\(^{XBP1s}\)/5xFAD triple transgenic animals.

SA3.2. In vitro analysis of the impact of XBP1 on APP metabolism.

Based on our positive results in vivo, we have included additional experiments in this project to characterize the impact of XBP1 on APP maturation and processing. These experiments are intended to obtain mechanistic insights to complement the in vivo analysis. We took advantage of the mouse neuroblastoma cell line (N2a), where we knocked-down XBP1 using stable delivery of an shRNA with lentiviruses. In addition, we were able to transiently overexpress the spliced form of XBP1 (XBP-1s) to perform gain-of-function experiments, in addition to use a truncated form of XBP-1 (XBP1 DN) as control.
We transfected control (shLUC) and knocked-down for XBP-1 (shXBP-1) cell lines with a construct that express human APP fused with GFP, under the control of a constitutive promoter (Figure 10A). After 48 hours post-transfection, we detected the total levels of APP. We observed that APP levels were increased when XBP1s was expressed (Figure 10B). Subsequently, the total levels of APP were dramatically decreased with the knockdown of XBP1, and this phenotype was partially rescued by overexpressing the same construct XBP-1s.

Next, we performed experiments to evaluate half-life of APP in cells overexpressing XBP1s or transfected with empty vector as control (pcDNA3). We treated cells with cycloheximide (CHX) that arrest protein synthesis and then measure APP stability (Figure 11A). We observed that overexpression of XBP1s significantly increased the half-life of APP, suggesting that XBP1 affect the degradation of APP (Figure 11B). To identify the molecular process that are affected by the loss of function of XBP1 in APP metabolism, we treated the transfected cells with lysosomal and autophagy inhibitors (Figure 12A). We did not observe rescue of total levels of APP in the shXBP1 cell line. Another possible pathway of degradation is the proteasomal pathway. Thus, we treated cells transfected APP-GFP with MG132, a proteasomal inhibitor (Figure 12B and 12C). We observed a partially rescue in the cell line deficient for XBP1. This result suggests that the deficiency of XBP1 alters the proper degradation of APP by the proteasome.

Finally, we took advantage of human neuroglioma cell line H4, which were engineered to stably express APP fused with GFP reporter. We performed knocked-down of XBP1 and we observed the same phenotype described before in N2a cell line (Figure 13A). Also, in this cell line it was possible to assay the maturation of APP, because it is feasible to detect both mature (upper) and immature forms of APP (lower). Moreover, the treatment with tunicamycin (Tm, Figure 13B), that inhibit the N-glycosylation, affected the electrophoretical migration patterns of APP and this pattern was similar to the one observed in the shXBP1 without treatment (basal condition). We detected the localization of APP in a normal lysosomal pattern in the shLUC cell line (Figure 13C), and the subcellular distribution was altered to a Golgi apparatus-like distribution and endoplasmic reticulum (ER) in absence of XBP-1 expression. Taken together, this data indicates that deficiency of XBP1 leads to alteration in the early maturation of APP in the ER that promotes its degradation by the proteasome.

We also measured the expression of AD-related genes in XBP1 knockdown cells at basal levels or after treatment with the ER stress agent tunicamycin (Figure 14). As positive control, we monitored the expression levels of XBP1 mRNA, the XBP1s-target gene EDEM1, and CHOP as an XBP1-independent target (Figure 14A). Genes such as CDK5, UBQLN1 and NCSTN did not appear to be regulated under ER stress. Remarkably, most AD-related genes (APBA3, APBB3, PSENEN and PSEN1) were upregulated after induction of ER stress (Figure 14B), where CDK5RAP3 (Figure 14C) showed a high dependency on XBP1 expression in the H4 cells, similarly to the data obtained in TgXBP1s mice.
OTHER ACHIEVEMENTS OF THE PROJECT:
- Research visit(s) to other institution(s).
- Outreach activities related to the project’s main topic.
- Any other contribution, not addressed elsewhere, that you consider important.

The maximum length for this section is 1 page. (Arial or Verdana, font size 10).

1.- Short stays:

During the development of my postdoctoral project I was able to strengthen and establish collaborations with prestigious international laboratories. In 2014, I did a short stay in the Laboratory of Protein Misfolding Disorder lead by Dr. Claudio Soto at the University of Texas Health Science Center at Houston McGovern Medical School Department of Neurology. Additionally, during the third year of the project, I had the opportunity to perform a short stay in the laboratory of Dr. Jeroen Hoozemans at UV University in Amsterdam, The Netherlands, who is an expert in histopathology of Alzheimer and ER stress markers. This collaboration allowed us to strengthen and increase our knowledge of Alzheimer and translational investigation, principal aim in my new Initiation Fondecyt Grant recently founded.

2.- Outreach activities:

I am active member of Chilean Alzheimer corporation COPRAD (www.coprad.cl). Here, I am involved in outreach activities to close the Chilean population with the science focused in neurodegeneration.

3.- Other publications:

During the development of my project I also collaborated for the production of additional ISI publications in the topic of amyloidogenic protein and Alzheimer's disease.

As an example:
INFORME DE EVALUACION DEL (DE LA) INVESTIGADOR(A) PATROCINANTE

NOMBRE: ______ Claudio Hetz ________________________________

Durante estos tres años en que Claudia ha desarrollado su proyecto de postdoctorado en mi laboratorio, ella se ha desempeñado de manera satisfactoria, mostrando gran independencia intelectual y capacidad de trabajar en equipo. En este tiempo Claudia ha participado en 6 publicaciones y tres de ellas como primera autora en revistas como *Frontiers in Aging Neuroscience*, Brain y Current Biology. En estos momentos estamos preparando y enviando dos publicaciones más relacionadas con su trabajo postdoctoral y colaboraciones.

Claudia, durante el primer año de proyecto, realizó una estadía de investigación en el Laboratorio de Protein Misfolding, dirigido por nuestro colaborador cercano Claudio Soto en Houston. El Dr. Soto es el director de un centro de neurodegeneración y posee un laboratorio de vasta experiencia en el emergente campo de las enfermedades neurodegenerativas, y en el cual Claudia recibió entrenamiento en la Enfermedad de Alzheimer y Priones. Adicionalmente, Claudia continúa generando publicaciones con el Dr. Soto en trabajos relacionados con la Enfermedad de Alzheimer y Priones.

Continuando con su extraordinario trabajo, durante este tercer año de ejecución de su proyecto postdoctoral, Claudia realizó una estadía en Holanda, Ámsterdam, específicamente en el laboratorio del Dr. Jereon Hoozmans, quien es un experto neurohistopatólogo en Alzheimer y marcadores de stress celular. Dada esta experiencia y pasantía, Claudia además de adquirir gran conocimiento en el área de cerebros humanos e histopatología, logró fortalecer una nueva colaboración muy potente en el área de Alzheimer e investigación traslacional.

La experiencia, énfasis y rigurosidad de Claudia no solo ha contribuido a desarrollar de manera exitosa su entrenamiento postdoctoral, sino también ha sido de valiosa ayuda para otros proyectos que se desarrollan en mi laboratorio. Finalmente, Claudia ha asumido importantes tareas relacionadas con el funcionamiento general del laboratorio, dejando de manifiesto su gran capacidad de trabajo y organización. Adicionalmente, Claudia ha formado estudiantes en unidades de investigación de pre-grado de la carrera de Medicina y otras carreras como biología y farmacología. En este momento, Claudia es co-tutora de una tesista de pre-grado de la carrera de bioquímica de nuestra institución.

En resumen, considero que el trabajo de Claudia ha sido satisfactorio y acorde con el nivel exigido. Sin duda, Claudia es una excelente investigadora que ha aportado enormemente a la investigación en mi grupo, conduciendo tanto su proyecto como otros relacionados con la Enfermedad de Alzheimer.

Para finalizar, gracias al éxito y dedicación de Claudia durante su estadía post-doctoral en mi laboratorio fue que ella se adjudicó el Concurso Iniciación en Investigación 2016 y con esto el inicio de su joven carrera científica independiente.
Firma Investigador(a) Patrocinante

Fecha: 17 de octubre del 2016
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<td>Duran-Aniotz, C.; Martínez, G.; Hetz C.</td>
<td>Frontier Aging Neuroscience</td>
<td>Memory loss in Alzheimer's disease: are the alterations in the UPR network involved in the cognitive impairment?</td>
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<td>Torres, M; Matamala, JM; Duran-Aniotz, C; Cornejo, VH; Foley, A; Hetz, C.</td>
<td>Virus Res</td>
<td>ER stress signaling and neurodegeneration: At the intersection between Alzheimer's disease and Prion-related disorders.</td>
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**Estado de la publicación a la fecha**: Publicada

**Otras Fuentes de financiamiento, si las hay**:

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Archivo(s) Asociado(s) al artículo:


Enviá documento en papel: no

Archivo(s) Asociado(s) al artículo:

ER_stress_AD_and_Prion._Torres_et_al._2015._Virus_Res.pdf

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<td>Commentary: XBP-1 Is a Cell-Nonautonomous Regulator of Stress Resistance and Longevity.</td>
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OTRAS PUBLICACIONES / PRODUCTOS

Sin información ingresada.

CONGRESOS

N°: 1
Autor (a)(es/as): Duran-Aniotz, C; Espinoza, S; Foley, A; Cornejo, VH; Martinez, G; Vidal, R; and Hetz, C.
Unfolded protein response (UPR) regulates the accumulation of Amyloid beta deposits in experimental model of Alzheimer’s disease

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A continuación se detallan los anexos físicos/papel que no se incluyen en el informe en formato PDF.