N° PROYECTO: 3140110  
DURACIÓN: 3 años  
AÑO ETAPA: 2016  

TÍTULO PROYECTO: C13ORF18/BECLIN1-INTERACTING PROTEIN (BCI): DEFINING THE ROLE OF A NOVEL AUTOPHAGY-RELATED PROTEIN TO AMYOTROPHIC LATERAL SCLEROSIS

DISCIPLINA PRINCIPAL: BIOLOGIA CELULAR  
GRUPO DE ESTUDIO: BIOLOGIA 2  
INVESTIGADOR(A) RESPONSABLE: MELISSA CALEGARO NASSIF

DIRECCIÓN:
COMUNA:  
CIUDAD: SANTIAGO  
REGIÓN: METROPOLITANA

FONDO NACIONAL DE DESARROLLO CIENTIFICO Y TECNOLOGICO (FONDECYT)
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INFORME FINAL
PROYECTO FONDECYT POSTDOCTORADO

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: To define the role of BCI and its interaction with Bcn1 in the autophagy pathway.</td>
<td>TOTAL</td>
<td>We confirmed the formation of a complex between BCI (hereafter called Rubicon-like, as updated in protein data sets) and Beclin1 (Bcn1) by immunoprecipitation and microscopy assays. We found that RubiconL interacts with Rubicon, a protein from its same family, and UVRAG, a member from autophagosome maturation complex with Bcn1 and Rubicon. Our macroautophagy (MA) flux experiments in motoneuron NSC34 cells provide evidences for a negative regulation of RubiconL on the pathway, which was confirmed by posterior experiments evaluating wild-type and mutant SOD1 aggregation. We also performed experiments evaluating the role of RubiconL on neuronal differentiation, showing that overexpressing of RubiconL in differentiated motoneuron cell line decrease the neurites formation. By bioinformatic analysis, we found some putative domains (e.g. putative BAG3 domain) that could explain these results and other phenotypes, which I aim to explore in the next step of our study (Initiation FONDECYT 2016).</td>
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<td>Specific Aim 2: To assess the impact of BCI on the aggregation, toxicity, and subcellular distribution of mutant SOD1 and TDP-43 in cellular models of ALS.</td>
<td>TOTAL</td>
<td>In order to address this aim, we generated motoneuron cell lines lacking RubiconL (by using short hairpin RNA, shRNA) and overexpressing RubiconL-V5 tagged. Vectors encoding wild-type and mutant SOD1, gene associated to familial ALS, were overexpressed in these lines and we could observe a spontaneous aggregation and perinuclear localization of wild-type SOD1 in both knockdown (KD) and overexpression of RubiconL. In addition, mutant SOD1 (G85R and G93A) presented an increased aggregation and co-localization with RubiconL-V5 in perinuclear localization. In KD cells, when we reconstituted the RubiconL levels with a vector encoding human RubiconL, we observed normal aggregation levels of mutant SOD1 and non-aggregation of wild-type SOD1. Of note, cells KD to RubiconL presented decreased viability when compared to scrambled expressing cells. Overall, we concluded that highly regulated levels of RubiconL is necessary to maintain the homeostasis at least in motoneurons.</td>
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<td>3</td>
<td>Specific Aim 3: To determine the expression of BCI in the progression of experimental models of ALS.</td>
<td>TOTAL</td>
<td>To understand the involvement of RubiconL in ALS pathogenesis, we evaluated its levels in wild-type mice and in two ALS mouse models. RubiconL mRNA displayed higher expression in the central nervous system (CNS) when compared to muscle or liver, similar to Rubicon. To evaluate the expression of RubiconL during ALS pathology we employed two familial ALS mouse models, SOD1G93A and TDP43A315T transgenic mice, both reported to display ALS disease features. We assessed RubiconL and Rubicon levels in the spinal cords (SC) of symptomatic mice. While RubiconL mRNA levels were not changed, RubiconL protein levels were significantly diminished in the spinal cords of both transgenic mice, at the end stage of the disease. Rubicon levels, however, were not changed. We then had the opportunity to evaluate the levels of RubiconL in human postmortem SC samples from sporadic ALS patients. We observed the same profile: diminished levels of RubiconL protein compared to health controls.</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.

Specific Aim 1: Bioinformatic analysis revealed that RubiconL contains a novel defined ring zinc-finger domain (Zf-Ring_9) also presented in Rubicon, PLEKHM1 (Pleckstrin homology domain-containing family M member 1), PLEKHM3, and DEF8 (Differentially expressed in FDCP 8 homolog), which are therefore grouped together as a protein family. It is probable that RubiconL has functions in membrane trafficking processes as well as macroautophagy (MA), such as its Rubicon and PLEKHM1. However, RubiconL does not present the PH or RUN domains. In addition, the N-terminus of RubiconL has no apparent homologies.
to other known proteins. We found putative domains in its sequence such as Bag3 domains, instead, and we plan to explore this possibilities in the next step of this project, under FONDECYT Iniciación 2016 support (#11160288).

Specific Aim 2: In the original initial project, we planned to perform the same group of experiments performed to SOD1 to TDP-43. We had some preliminary results, but, in order to finish the manuscript with a detailed study of RubiconL and SOD1, they are not finished. On the other hand, we verified the levels of RubiconL in a transgenic mouse model of TDP-43 and showed a profile similar, with decreased levels at symptomatic stage of the disease (Specific Aim 3). We will continuous with TDP-43 and RubiconL in vitro, with collaboration with Dr. Ute Woehhbier.

Specific Aim 3: This specific aim achievements were a result of a collaborative effort integrating laboratories involved in ALS disease research in Chile and USA, which caused a delay in the submission of the final manuscript. The mice used were maintained in the Universidad Mayor mice room (Bioterio). For the TDP-43 transgenic mice, I am very grateful to Dr. Soledad Matus and Dr. Ute Woehhbier (U. Mayor). Moreover, we think that the paper would present a strength if we could correlate the results that we found in the network analysis with the analysis of postmortem tissues from humam ALS patients. For the human ALS postmortem tissues, I am very thankful to Dr. Ute Woehhbier (U. Mayor), Dr. Claudio Hetz (U. Chile), Dr. Danilo Medinas (U. Chile), Dr. Daryl Bosco and Dr. Robert Brown (University of Massachusetts Medical School; UMMS).
RESULTS OBTAINED:
For each specific goal, describe or summarize the results obtained. Relate each one to work already published and/or manuscripts submitted. In the Annex section include additional information deemed pertinent and relevant to the evaluation process. 

The maximum length for this section is 5 pages. (Arial or Verdana, font size 10).

Specific Aim 1: To define the role of BCI and its interaction with Bcn1 in the autophagy pathway. In 2010, a large-scale proteomic study of the macroautophagy (hereafter called autophagy) network proposed BCI (hereafter called RUBCNL, by updates in protein data sets - Rubicon-like) as a new interacting partner of Beclin1 (Becn1), an interaction that Dr. Patricio Manque found by convergent analysis in a ALS context (manuscript submitted to Nature Journal). To interrogate this interaction, we first co-expressed V5-tagged mouse RUBCNL (mRUBCNL-V5) with MYC or FLAG-tagged Becn1 (MYC-Becn1 or FLAG-Becn1). Besides their co-localization (Fig. 1A and B) in the mouse motoneuron cell line NSC34, we also observed the formation of a protein complex by immunoprecipitation (IP) experiments in HEK293T cells using the V5-tag, IP endogenous Becn1 and MYC-Becn1 (Fig. 1C and D). Furthermore, mRUBCNL-V5 presented a vesicular profile that partially co-localized with lysosomes and endosomes (Fig. 1E and F). Our results demonstrate that RUBCNL and Becn1 are components of the same complex and suggest that RUBCNL participates in autophagy. The expression level of many autophagy genes, e.g. Becn1, is generally upregulated upon activation of this pathway. We assessed the possible regulation of RUBCNL expression under autophagy induction. RUBCNL mRNA was increased after treatment with rapamycin, similar to Becn1 mRNA (Fig. 1G). RUBCNL protein levels were also increased, similar to Becn1 and LC3B-II under activated autophagy (Fig. 1H). To investigate if RUBCNL expression affects autophagy we either increased RUBCNL levels by exogenous expression of mRUBCNL-V5 or depleted its levels by knockdown of endogenous mRUBCNL in NSC34 motoneuron cells. First, we depleted NSC34 cells of RUBCNL by targeting RUBCNL mRNA using a mix of short-hairpin RNAs (shRUBCNL A and B) (Fig. 1I). To evaluate the impact of RUBCNL in autophagy, we evaluated the autophagy flux under mRUBCNL knockdown. Briefly, we determined the levels of key autophagy markers after treatment of NSC34 cells with EBSS for different time periods in the presence or absence of lysosomal inhibitors. Down regulation of mRUBCNL decreased autophagy fluxes (Fig. 1J). Of note, Rubicon (RUBCN) levels were significantly reduced in cells expressing shRUBCNL compared to shCTRL cells. These results suggest that RUBCNL may have a stabilizing function towards RUBCN, and this function seems to be more important relevant under induction of autophagy than under basal conditions, since RUBCN levels are even more reduced under EBSS treatment (Fig. 1J). We also performed the autophagic flux under overexpressed levels of mRUBCNL-V5. Notable, we observed the same profile in LC3B-II reduction, suggesting a reduction in autophagosome formation as well (Fig. 1K). The increased levels of Becn1 could be a compensatory result to intent mitigates the inhibition in LC3B-II formation. Taken together, our results suggest that slight changes in RUBCNL endogenous levels negatively affect the autophagy pathway, most likely by interfering with the first step of autophagosome formation (manuscript submitted to Nature Journal). Of note, several examples in the literature showing decreased or excessive concentrations of proteins can lead to the same phenotype, a characteristic which is well described for proteins with scaffolding functions (reviewed in 1), including some proteins known to be associated with neurodegenerative diseases, such as optineurin (ALS) and LRRK2 (Parkinson’s disease) 2,3.

Specific Aim 2: To assess the impact of BCI on the aggregation, toxicity, and subcellular distribution of mutant SOD1 and TDP-43 in cellular models of ALS. To determine the relevance of RUBCNL to ALS pathogenesis, we determined the impact of its expression in SOD1 aggregation. Knocking down mRUBCNL in the NSC34 motoneuron cell line led to increased SOD1 aggregation mutant SOD1 using western blot analysis (Fig. 2A). Interestingly, we also observed the spontaneous aggregation of wild-type SOD1 upon knocking down mRUBCNL (Fig. 2A), a phenomenon described in sALS cases 4. Practically identical results were obtained using filter trap (Fig. 2B). Since our shRNA constructs target exclusively mouse RUBCNL (mRUBCNL), we restored RUBCNL levels using exogenous expression of human RUBCNL (hRUBCNL-V5). The re-expression of hRUBCNL could recover normal levels of SOD1 aggregation levels to a similar extent to control cells (Fig. 2A and B). Furthermore, confocal microscopy of SOD1 aggregates confirmed these findings: depletion of RUBCNL led to an increased number of aggregates formed by SOD1593A (Fig. 2C), whereas it had dramatic effects on SOD1WT which formed large de novo inclusions similar in size to aggregates observed for mutant SOD1 (Fig. 2C).
Our results indicate an important role for RUBCNL in maintaining proteostasis by promoting aggregate removal, specifically of SOD1 aggregates during ALS pathogenesis.

**Specific Aim 3: To determine the expression of BCI in the progression of experimental models of ALS.** With the aim to understand the involvement of RUBCNL in ALS pathogenesis, we first evaluated the levels of RUBCNL in wild-type mice and in two familial (fALS)ALS mouse models. RUBCNL, RUBCN and Becl1 mRNA levels were assessed by real time PCR in different mouse tissues: cortex, cerebellum, hippocampus, spinal cord (SC), muscle, and liver, obtained from eight wild-type C57BL/6 mice (4 males and 4 females) 100 days of age. RUBCNL mRNA displayed higher expression in the central nervous system (CNS) when compared to muscle or liver, similar to RUBCN, whereas Becl1 showed highest expression in the hippocampus, confirming previous findings (Fig. 2E) 5. To evaluate the expression of RUBCNL during ALS pathology we employed two fALS mouse models, SOD1<sup>G93A</sup> and TDP43<sup>A315T</sup> transgenic mice (SOD1<sup>G93A</sup>-Tg and TDP43<sup>A315T</sup>-Tg, respectively), both reported to display ALS disease features 6,7. We assessed RUBCNL and RUBCN levels in the SCs of symptomatic transgenic mice compared to their respective non-transgenic (non-Tg) littermates. While RUBCNL mRNA levels were not changed (Fig. 2F), RUBCNL protein levels were significantly diminished in the SCs of both SOD1<sup>G93A</sup>-Tg and TDP43<sup>A315T</sup>-Tg mice compared to their respective non-Tg controls (Fig. 3A and B). We then determined the levels of RUBCNL in the human ALS pathology in postmortem SC samples from sporadic ALS (sALS) patients (Table 1, available in Annex). Remarkably consistent with our findings in fALS mouse models, we found a significant decrease of RUBCNL protein levels in the lumbar SC of sALS patients compared to age-matched healthy control subjects (Fig. 3E). A similar trend was observed in the thoracic SC (Fig. 3D), yet no tendency was found in the cervical SC (Fig. 3C), however for both cervical and thoracic sections tissue from only two control cases were available to us. These findings indicate that at least the lumbar region of the SC of sALS patients displays a significant loss of RUBCNL protein levels during disease.

In summary, we obtained consistent results for RUBCNL in sALS patients and both fALS mouse models during ALS pathology. Together with the observation that the loss of RUBCNL leads to protein aggregate accumulation, our data suggests a potential role of RUBCNL during the disease and at least partially confirms our initial prediction.


References:

Figure 1

A) Images showing different staining patterns for MYC-Becn1 and mRUBCNL-V5.

B) Bar graph showing Pearson's Coefficient for Becn1.

C) Western blot analysis for V5 and Becn1 endosome.

D) Table showing Molecular Weight (kDa) for different proteins.

E) Immunofluorescence images for Beclin1 and V5.

F) Graph showing Pearson's Coefficient for Lyosome and Endosome.

G) Graph showing Pearson's Coefficient for RUBCNL and Beclin1.

H) Western blot analysis for shCTRL and shRUBCNL.

I) Graph showing ACT activity for Mock and mRUBCNL-V5.

J) Western blot analysis for EBSS and Lys. I.

K) Western blot analysis for mRUBCNL, Becn1, RUBCN, LC3B-I, LC3B-II, V5, and β-Actin.

Figure 1
Figure 2

A. Western blot analysis showing the effect of hRUBCNL-V5 and shRUBCNL on SOD1 (-DTT) and (+DTT) levels. The blots are labeled with MW (kDa) and include hRUBCNL-V5 and shRUBCNL.

B. Bar graph showing the expression levels of SOD1 WT, EGFP, SOD1 G93A, hRUBCNL-V5, and HSP90 under shCTRL and shRUBCNL conditions.

C. Immunofluorescence images of SOD1 WT and SOD1 G93A in control and shCTRL conditions.

D. Immunofluorescence images of SOD1 G93A in control and shCTRL conditions.

E. qRT-PCR analysis showing the expression levels of RUBCNL, RUBCN, and Becn1 in various tissues (Spinal Cord, Cortex, Hippocampus, Liver) under different conditions.

F. Graph showing the expression levels of mRUBCNL/Actin mRNA in non-Tg, SOD1 G93A-Tg, TDP43 A51T-Tg conditions.

Figure 2
Figure 3

A

B

C

D

E

\textbf{Figure 3}
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. Collaboration in students’ laboratory training:
   During the summer vacations, we receive undergraduate for one month work in the laboratory addressing interesting topics that could improve their skills and increase their interest in science, giving the opportunity to work in a real laboratory. In addition, these topics could become later theirs undergraduate thesis. I had the pleasure to coach one student from Mexico in the laboratory from December-January 2017, three students from U. Mayor Biotechnology career from December-January 2016, and two from the same career from December-January 2015.

2016
During the summer (15th December to 13th January, 2017), a student from Mexico was in our laboratory under my supervision, working on molecular techniques that would help her in her thesis in Mexico (Report in Anexos).

Frida Alexa Aguilar Sánchez

2015
During the summer (December and January, 2016), three students were under my supervision in the laboratory. They investigated some other aspects of BCI (KIAA0226L) protein (Report II):

- Octavia Santis (Role of BCI in phagocytosis)
- Felipe Grunenwald (Role of BCI in infection)
- Felipe Garcia (Role of BCI in cancer cell line).

Felipe Garcia was working in the laboratory this last summer as well, preparing his thesis in the same topic.

2014
This year, during December and January, 2015, two students were under my supervision in the laboratory working on cell culture and evaluating BCI roles in (Report I):

- Carla Daniela Gonzalez (Role of BCI in SOD1 aggregation)
- Javiera Arcos (Role of BCI in infection)

Carla did her thesis project in PUC, under Francisca Broffman supervision, and I had the opportunity to be part of her evaluation committee.

Javiera is finishing her thesis under Dr. Patricio Manque supervision in our laboratory.

2. Participation in undergraduate thesis/qualification exam evaluation committee:

2.1. Allan Arenas
   “Regulación de la actividad del receptor activado por proliferadores peroximales-a (PPAR-a) hepático por la hormona tiroidea (T3) 24th January 2017, 2 pm.

2.2. Carla Daniela González Moreno
   “Estudio de la fosforilación de Rab11 inducida por el receptor TRK en células HEK293” 7th December 2016, 10 am.

2.3. Camila Avendaño Costas
   “Estudio de la relación entre microbiota intestinal y la obesidad en un modelo experimental de raton” 28th June 2016, 11.30 am.
## ARTÍCULOS

Para trabajos en Prensa/ Aceptados/Enviados adjunte copia de carta de aceptación o de recepción.

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(Pagina 1268-1269)

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**Otras Publicaciones / Productos**

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<td>BCI - a new protein involved in the autophagy pathway.</td>
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Nombre del Congreso : Autophagy in Stress, Development & Disease (GRC ) Gordon Research Conference

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Ciudad : Ventura

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País : CHILE

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Título (Idioma original) : Bci a new player involved in SOD1 aggregation

Nº : 5
A continuación se detallan los anexos físicos/papel que no se incluyen en el informe en formato PDF.

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