GLUCOCORTICOID RECEPTOR BETA (GR-β) INDUCES AUTOPHAGY

Farías, M.B.1,2; Bernal-Sore, I.1,2; Pennanen, C.1; Mellado, R.3; Troncoso, R.1,2

1Advanced Center for Chronic Disease (ACCDiS), Facultad de Ciencias Químicas y Farmacéuticas and 2Instituto de Nutrición y Tecnología de los Alimentos (INTA), Universidad de Chile, Santiago, Chile. 3Departamento de Farmacia, Facultad de Química, Pontificia Universidad Católica de Chile, Chile.

Glucocorticoids (GC) are steroid hormones important for maintenance of basal and stress-related homeostasis. Synthetic glucocorticoids are used for treating inflammatory and autoimmune diseases. The effects of glucocorticoids are mediated by the glucocorticoid receptor (GR). GR is mostly expressed as two alternately spliced isoforms α and β. The GR-α is the classic receptor, binding to glucocorticoids and mediating most of the known glucocorticoid actions, while that GR-β cannot bind GC, but the synthetic drug RU486 was able to bind it and modulate its transcriptional activity. Autophagy is a conserved process that involved the degradation of cellular components to maintain energy levels and to provide macromolecules for the synthesis of complex structures, thereby promoting cell metabolism, homeostasis, and survival. It is know the function of glucocorticoid in autophagy induction, however the role of GR-β is not understood. The proposal of this work is determine GR-β effect on autophagy.

Material and methods: To assess the effect of GR-β and RU486 on autophagy induction. GR-β was overexpressed into HeLa and U2OS-GFP-LC3 cell lines; the U2OS cell line does not express detectable levels of endogenous GR. To study autophagy induction the GR-β overexpressed or RU486 treated cells, LC3 processing and p62 protein levels were assessed by immunoblot, GFP-LC3 puncta was determined by fluorescent microscopy. Autophagy flux was assessed by exposure to chloroquine.

Results: Overexpression of GR-β in HeLa and U2OS cells show an increase in LC3 processing, which correlates with an increase in GFP-LC3 dots and augmented autophagy flux in U2OS cells. On the other hand, the treatment with RU486 increases LC3 processing but not autophagy flux only in HeLa cells. Finally, RU486 was not able to inhibit the increase on GR-β-induced LC3 processing in U2OS cells.

Conclusions: Altogether, these results suggest that the expression of GR-β induces an increase in autophagy. However, RU486 is not able to regulate GR-β-induced autophagy.

Acknowledgements: FONDECYT 11130285 (RT) and FONDAP 15130011 (RT) supported this work.

Keywords: Autophagy, Glucocorticoid receptor, RU486