Cloning and characterization of the Promoter of the Insulin Receptor Substrates (IRS1, IRS2)

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Diabetes and insulin resistance are associated with a higher risk of neurodegenerative diseases. Insulin signaling is mediated by insulin receptor substrates (IRS). Alterations in the expression of these proteins can result in insulin resistance. Previous studies showed changes in the levels of mRNA of IRS1 and IRS2 in situation of metabolic syndrome (Ribes-Navaro A. et al 2019).

In order to characterize the promoters that regulates the expression of these genes, we used bioinformatic tools. In addition, to determine the promoter activity, we cloned 1000bp the DNA region upstream the transcription starting site (TSS) into a reporter plasmid and monitor promoter activity by reporter GFP fluorescence.

Bioinformatic analysis reveals the presence of many HES1 factors binding sites in the IRS2 promoter, and very few within the IRS1 promoter. The differences within the promoter region may explain the different expression under the same stimuli of both IRSs mRNA. In addition, we observed that CpG islands were concentrated close to the TSS in both human IRS1 and IRS2 promoter, and disperse in rat promoters. The rat IRS1 promoter was successfully cloned, but showed low activity in HEK293 human cells.

Further studies are needed decipher mechanism underlying promoter activity. In addition human promoters will be cloned. Under the light of the present results, enhancers may be needed to increase promoter activity.

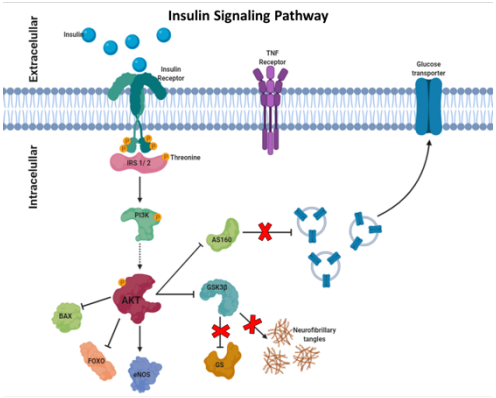


Figure 1. *Insulin signaling pathway in physiological conditions*.

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2. Ribes-Navarro, A (2019). Correction to: Abscisic Acid Supplementation Rescues High Fat Diet-Induced Alterations in Hippocampal Inflammation and IRSs Expression. *Molecular neurobiology*, *56*(5), 3833-3833.
3. Albert-Gasco, H (2019). Central relaxin-3 receptor (RXFP3) activation impairs social recognition and modulates ERK-phosphorylation in specific GABAergic amygdala neurons. *Brain Structure and Function*, *224*(1), 453-469.
4. Albert-Gascó, H (2017). Central relaxin-3 receptor (RXFP3) activation increases ERK phosphorylation in septal cholinergic neurons and impairs spatial working memory. *Brain Structure and Function*, *222*(1), 449-463.
5. Sánchez-Sarasúa, S (2016). The effect of abscisic acid chronic treatment on neuroinflammatory markers and memory in a rat model of high-fat diet induced neuroinflammation. *Nutrition & metabolism*, *13*(1), 73.



PhD Student Paola Valero is actually enrolled in the doctoral program in Biomedical Sciences and Health of the University Jaume I, and she is participating within the line of research in Neurobiotechnology, which is focused on the study of the insulin signaling pathway, specifically the ways of regulating the insulin receptor substrates 1 and 2, and their connection with neurodegenerative diseases such as Alzheimer's disease. Thanks to her degree in Biochemistry and her recent master's degree in cellular and molecular biology (specialization in neurobiology), she has acquired a medium-high knowledge in neurobiology, cell biology of the neuron, neurochemistry, aging and neurodegeneration.

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