Poster

Genetic factors involved in the cognitive impairement of Alzheimer's disease patients

González Palma, Laura Marina (1), Royo Sánchez-Palencia, José Luis(1,*)

(1)Departmento de Especialidades Quirúrgicas, Bioquímicas e Inmunología. Facultad de Medicina. Dirección Bulevar Louis Pasteur, 32, 29010 Málaga.

Tutor académico: Flor Parra, Ignacio

Keywords: Alzheimer disease, SIRPB1, DAP12

ABSTRACT

Motivation: Alzheimer's disease is linked to the extracellular accumulation of ß-amyloid, an event closely related to the phagocytic activity of microglia. Some authors have linked ß-amyloid phagocytosis to the activity of the membrane protein SIRPB1, which may be mediating the process via DAP12, as well as other receptors previously described as TREM2. In our group, we have described a genetic variant within the open reading frame of SIRPB1. It is a 30.1 kb insertion, which alters the structure of the gene and affects the gene maturation isoforms, modifying both the extracellular domain and the transmembrane domain with which it interacts with DAP12. The role of this variant in microglial phagocytosis and its possible contribution to the molecular etiology of Alzheimer's disease remains to be determined.

Methods: The transmembrane sequences of DAP12, TREM2 and the two isoforms of SIRPB1 potentially affected by the insertion have been cloned. The BATCH two-hybrid system has been used to quantitatively and qualitatively determine the differential intramembrane affinity of each domain for DAP12. To do this, an assay has been carried out to measure the ß-galactosidase activity, in addition to the visualization of the blue color deposition in X-gal medium. For the data analysis, the ImageJ software was used to quantify the color intensity and IBM SPSS for the statistics.

Results: The two-hybrid assays support the interaction described in the literature between DAP12 and TREM2, and between DAP12 and the SIRPB1 variants. Furthermore, the results suggest a differential binding to DAP12 by the transmembrane domains of the SIRPB1 isoforms under study.

Conclusions: The fact that the interaction between the different isoforms of SIRPB1 and DAP12 varies may lead to phagocytic responses of dissimilar intensity, resulting in an uneven accumulation of ß-amyloid. This could partly account for the variability observed in different Alzheimer's disease patients.

REFERENCES

Blennow, K., Leon, M. J. De and Zetterberg, H. (2006) 'Alzheimer' s disease.', 368, pp. 387–403. doi: 10.1016/S0140-6736(06)69113-7.

Royo, J. L. et al. (2018) 'A common copy-number variant within SIRPB1 correlates with human out-of-Africa migration after genetic drift correction', PLoS ONE, 13(3), pp. 1–16. doi: 10.1371/journal.pone.0193614.

Tomasello, E. et al. (2000) 'Association of signal-regulatory proteins β with KARAP/DAP-12', European Journal of Immunology, 30(8), pp. 2147–2156. doi: 10.1002/1521-4141(2000)30:8<2147::AID-IMMU2147>3.0.CO;2-1.