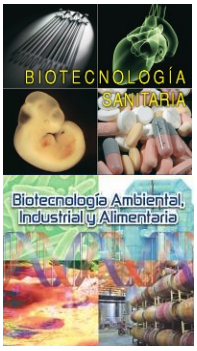
Poster



Autoinflammatory and immunodeficiency due to loss of function mutation in ELF4

Ortiz Ramírez, Ana(1), Blanco Lobo, Pilar(1), De Felipe, Bea(1), Moreno Fuentes, David (1), Olbrich, Peter(1), Neth, Olaf*(1), Rodríguez, Alejandro(2)

(1) Pediatric Infectious Diseases, Rheumatology and Immunology Unit, Hospital Universitario Virgen del Rocío, Institute of Biomedicine of Seville (IBiS), RECLIP, Seville, Spain. Avda. Manuel Siurot s/nº41013

(2) Pediatric Gastroenterology Unit, Hospital Universitario Virgen del Rocío

Tutor académico: Victor Alvarez Tallada

Keywords: Deficiency in ELF4-X linked; JAK/STAT pathway; JAK inhibitors

ABSTRACT

Background: Inborn errors of immunity (IEI) are defined as monogenetic germline defects characterized by increased susceptibility to infections, immune diseases, allergies, and cancers. Recently, a new condition called "deficiency in ELF4, X-linked" (DEX) has been identified as a disease of immune dysregulation [1]. DEX patients commonly manifest symptoms such as fevers, along with various inflammatory manifestations that primarily affect the gastrointestinal tract, as well as notable involvement of the skin [2, 3]. Despite the identification of the condition and the involvement of the ELF4 gene, the specific biological processes and mechanisms by which DEX and ELF4 function results in the observed symptoms are not completely understood. In addition, a personalized therapy is needed due to the complexity of the disease.

Objective: Here, we aim to explore the link between ELF4 deficiency and the pro-inflammatory state resulting in the clinical manifestations of these patients. We also pursue to evaluate the ex vivo effects of JAK inhibition.

Methods: Using flow cytometry, RT-qPCR and ELISA techniques, the levels of STAT1 and pSTAT1 were examined in IFN stimulated cells obtained from ELF4 deficient, STAT1 GOF patients and healthy controls. By using nCounter FLEX (NanoString) platform and Luminex assay, we quantified expression levels of IFN-response genes and serum cytokine levels.

Results: ELF4 deficient and STAT1 GOF patients presented similar phenotype characterized by increased STAT1 and pSTAT1 levels in response to INFa and IFNg. STAT1-downstream gene expression and CXCL10 secretion were elevated compare to healthy controls. Ex vivo treatment with Ruxolitinib (JAK1/2 inhibitor) reduced STAT1 phosphorylation in ELF4 and STAT1 GOF patient cells.

Conclusion: These results have improved the comprehension of ELF4 role in autoinflammatory syndromes. However, further investigations are required in order to fully understand the impact of ELF4 deficiency in immune dysregulation and the potential targeted therapies that could benefit those patients including JAK inhibitors.

REFERENCES

1. Tangye et al. (2022) Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. Journal of Clinical Immunology, 42(7), 1473-1507. https://doi.org/10.1007/s10875-022-01289-3
2. Olyha et al. (2024) “Deficiency in ELF4, X-linked”: A monogenic disease entity resembling Behçet’s syndrome and inflammatory bowel disease. Journal of Clinical Immunology, 44(2).https://doi.org/10.1007/s10875-023-01610-8
3. Sun et al. (2023) A multicenter cohort study of immune dysregulation disorders caused by ELF4 variants in China. Journal of Clinical Immunology, 43(5), 933–939. https://doi.org/10.1007/s10875-023-01453-3