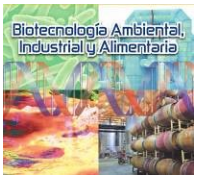
Poster



Immune dysregulation in children with Down Syndrome and Janus Kinase inhibition as targeted therapy.

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ABSTRACT

Down Syndrome (DS), also known as Trisomy 21, is a genetic disorder that results from partial or complete third copy of chromosome 21. It is one of the most common genetic disorders worldwide affecting 6 million individuals. It is the leading cause of lifelong intellectual disability and is often associated with other clinical alterations [1], including cardiac and gastrointestinal anatomic defects, an increased incidence of Alzheimer's disease as well as a heightened vulnerability to infections.

DS has shown to be associated with inflammatory and autoimmune processes such as periodontitis, alopecia, dermatitis among others [2]. The fact that 4/6 Interferon (IFN) receptors are localized on chromosome 21 is currently an appealing hypotheses to explain the observed IFN hypersensitivity in DS population. A subset of DS individuals shares clinical manifestations with patients with Signal-Transducer and Activator of Transcription 1 gain-of-function (STAT1 GOF) patients, who also present IFN hypersensitivity and increased levels of STAT1 and its phosphorylated form (pSTAT1) [3]. Janus Kinase (JAK) inhibition has been a successful treatment for STAT1 GOF patients. However, its potential and effectiveness in Down Syndrome has not been explored yet. We here propose Baricitinib as a targeted therapeutic approach for a selected subgroup of DS patients with IFN hypersensitivity and clinical manifestations similar to the ones seen in patients with STAT1 GOF. Whole blood (WB) obtained from STAT1 GOF patients, DS individuals and healthy controls (HC) was stimulated with IFN αlpha/gamma in the presence of Baricitinib. Flow cytometry was performed using specific antibodies against CD14 (monocytes), CD3, STAT1 and pSTAT1. In parallel, PBMCs were stimulated with IFN alpha/gamma , and transcription levels of STAT1, CxCL10, SOCS1 and PD-L1 were evaluated by RT-PCR. According to previous studies [3], we found in DS individuals an increased gene dosage of IFNaR1 and IFNaR2. Furthermore, similar to STAT1 GOF patients some DS individuals present increased levels of STAT1 and pSTAT1 after stimulation compared to HC in CD14 and CD3 T cells. We also observed that ex vivo JAK inhibition was effective reducing this IFN hypersensitivity in DS cells similar to STAT1 GOF patients' cells. Taken together, Baricitinib a JAK1/2 inhibitor might represent a promising targeted therapy for a subgroup of DS with inflammatory and/or infectious manifestations.

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