ORT_02 - A variant found in the *RELA* gene in a patient with autoinflammatory disease: Inborn Errors of Immunity?

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Introduction: Inborn Errors of Immunity (IEI) are rare alterations in the immune system that cause increased susceptibility to infections, autoimmune diseases, autoinflammatory diseases, allergy, and/or malignancy. Recently two cases of *RELA* haploinsufficiency were described resulting in mucocutaneous inflammation due to impaired activation of NFκB (Nuclear factor-kappa B), a major inducer of inflammatory mediators, hyper-activated in autoimmune diseases.

Objective: In the present work, we aim to conduct a genomic-functional investigation in a patient with an autoimmune condition, characterized by frequent *Staphylococcus aureus* infections.

Methodology: Here we conducted a trio study of 15 years-old female patients with a history of recurrent skin and lung inflammations and antibiotic-resistant *S. aureus* infection, and her healthy father and mother. Whole blood samples from the family were collected for Whole Exome Sequencing (WES) followed by evaluation of trio by Sanger sequencing. Peripheral blood mononuclear cells (PBMCs) from the patient and healthy control were stimulated for 4 hours with *S. aureus* and cytokines IL-6 and IL-8 quantified in the culture supernatant using LATIM-Bio-Manguinho's in house assay. The total RNA was extracted followed by the synthesis of cDNA and quantitative PCR for *BCL2* and *RELA*. The whole mRNA was sequenced for the identification of differentially expressed genes (DEGs).

Results: The WES analysis demonstrated that patient presented a heterozygous mutation in *RELA* with a cytosine deletion at position 936 of the cDNA (c. 936delC) generating stop codon, resulting in a *de novo* mutation. In the absence of *S.aureus*, the patient's PBMC showed increased levels of *RELA* expression, IL-6, and IL-8, and decreased *BCL2* suggesting constant leukocyte activation. Under stimulation with *S. aureus* saturation response and apoptosis were evidenced by a decrease in *RELA* of IL-6 and IL-8 and an increase in *BCL2*. Gene expression analysis by RNAseq allows characterization and functional validation of this potential IEI case in *RELA*.

Conclusion: The genomic and functional data presented here corroborate the haploinsufficiency in *RELA*, configuring an EII related to recurrent *S.aureus* infections. This data expands the knowledge of pathogen-host interactions and aid future personalized therapy.

Keywords: Inborn Errors of Immunity; Nuclear factor-kappa B; Functional-genomics