DISCOVERY OF AN ALTERNATIVE GENETIC ETIOLOGY FOR JOB SYNDROME

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Background: The primary immune deficiency Job syndrome displays a classic phenotypic triad of eczematous dermatitis, recurrent skin and sinopulmonary infections and elevated serum immunoglobulin E (IgE). Heterozygous, dominant-negative mutations in the transcription factor STAT3 that cause a transcriptional loss-of-function (LOF) are the etiology in 75% of cases. Recent systematic genetic analysis of “unsolved” patients with this highly recognizable phenotype has uncovered additional autosomal recessive causes, including mutations in ZNF341 and the cytokine receptor gp130.

Materials/Methods: The patient was enrolled into the Undiagnosed Diseases Network for evaluation of a genetic cause of Job syndrome lacking a STAT3 mutation. Research immunophenotyping, trio exome sequencing, and RNA-sequencing were performed. Additional functional studies were conducted to evaluate cytokine signaling.

Results: The patient was a 26-year-old female with a life long history of eczema and severe, recurrent sinopulmonary infections. She had an NIH score of 66 (>40 suggestive of Job syndrome) due to a combination of immunologic and non-immunologic criteria. This included recurrent pneumonias, pneumatoceles, elevated IgE (3970 IU/mL), eosinophilia, onychomycosis, retained primary teeth, scoliosis, bone fractures, and a high-arched palate. Immunophenotyping demonstrated low Th17 cells, a characteristic of Job syndrome. Research trio exome sequencing uncovered a de novo mutation in gp130, predicted to lead to a truncated protein (p.L708*). RNA-sequencing suggested the mutant allele was increased compared to wild-type; transfection experiments into gp130-deficient cells revealed increased mutant protein. Cells from the patient displayed no STAT3 activation after stimulation with some, but not all, gp130-receptor family cytokines. An in vitro system demonstrated absent signaling through mutant gp130.

Conclusions: We report the discovery of a de novo mutation in the gp130 cytokine receptor in a patient with Job syndrome. Mutant gp130 is unable to transmit cytokine signals. Patient cells fail to activate STAT3 downstream of gp130-family cytokines, resulting in a phenocopy of LOF mutations in STAT3. Compound heterozygous missense mutations in gp130 have previously been reported to cause Job syndrome, but this is the first patient with Job syndrome secondary to a heterozygous truncating mutation in gp130. Efforts are ongoing to understand the mechanism by which mutant gp130 interferes with some, but not all, gp130-family cytokine signals.