Final report – Job Research Foundation – 2020 – 2022

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Project Title: " Impaired Epithelial Differentiation & Host Defense as a Mechanism for Pulmonary Complications in Job Syndrome Patients"

Project Summary

Job syndrome is a rare disease characterized by recurrent infections and elevated IgE levels (HIES). It is caused by an autosomal dominant de novo mutation in the STAT3 gene. Although the clinical manifestations extend over multiple systems in the body including the immune system, skeletal/dental system, and connective tissues, patients with job syndrome are particularly prone to developing pulmonary complications including bronchiectasis, pneumatoceles, bronchopleural fistulas, lung abscesses, and airway infections with bacterial and fungal pathogens.

The previous studies of Job syndrome were mainly focused on immune cells. An incompetent immune system is believed to primarily account for these lung manifestations. However, immunomodulatory therapies and bone marrow/hematopoietic stem cell transplantation were not sufficient to fully cure lung symptoms, suggesting that additional defects in other tissue compartments such as the airway epithelial mucosal barrier may also contribute to chronic fungal and bacterial infections associated with Job Syndrome. Numerous observations and publications have highlighted the critical role of the airway epithelial cells in fighting against infection and maintaining lung homeostasis. Mucous secretion and mucociliary transport together function to remove trapped pathogens. In addition, airway epithelial cells stand at the frontier of defense against invading microbes via constitutive host defense mechanisms and by the attraction of immune cells to the infected site. In later stages, airway epithelial cells also mediate adaptive immunity by recruitment of T- and B-lymphocytes. Therefore, understanding STAT3 mutation-associated pathophysiological changes in airway epithelial cells will inform further specific and effective treatments. With the award from Job Research Foundation, we have interrogated how AD-HIES STAT3 mutations impact airway epithelial cell differentiation and physiological functions.

We have generated a series of airway basal cell lines harboring the four most common AD-HIES STAT3 mutations (R382W, V463del, V637M, and Y657S). In addition, we derived primary airway basal cells from a Job Syndrome patient harboring a STAT3-S560del mutation and from mice harboring a STAT3-V463del mutation. We identified that AD-HIES STAT3 mutations

differentially blunt STAT3 protein phosphorylation, nuclear translocation, transcription activity, and protein stability, leading to insufficient STAT3 function in airway basal cells. To investigate if Job Syndrome patients have altered airway epithelial composition, we differentiated control and Job Syndrome airway basal cells on the air-liquid interface. The results suggested that AD-HIES STAT3 airway basal cells generated a significantly lower number of Ac-Tubulin^{+} ciliated cells but a higher number of MUC5AC^{+} goblet cells and CCSP^{+} club cells. As a consequence, coordinated mucociliary transport based on micro-optical coherence tomography imaging is lost. Notably, mucus hypersecretion and impaired mucocilliary clearance are hallmark features of CF and non-CF bronchiectasis. Furthermore, we observed that AD-HIES STAT3 airway epithelial cells lost the efficient bacterial killing ability and innate immune response. For example, in response to PA01 infection, AD-HIES STAT3 airway epithelial cells secrete a reduced level of antibacterial substances and proinflammatory cytokine and chemokine to control pathogens. In addition, AD-HIES airway epithelial cells fail to support vigorous neutrophil infiltration induced by pathogenic infection. All of these epithelial defects likely contribute to chronic fungal and bacterial infection and bronchiectasis that is observed in Job Syndrome patients.

In summary, our study defines the pathophysiological mechanisms underlying epithelial cell anomalies in Job Syndrome, adding to our understanding of the complex biology of this disease. We emphasize that epithelial cell host defense defects and possible impairment in tissue regeneration after injuries are additional risk factors in impacting the development and progression of lung complications in Job Syndrome. From the therapeutic point of view, we advocate that more broadly therapeutic approaches must be addressed in Job Syndrome treatment, including at least therapies that encompass both the epithelial cells and immune cells. For example, inhalable pharmacological activation of STAT3 signaling agonists may help to restore normal airway epithelial cell architecture, host defense functions, and injury repair. Gene therapy or stem cell-based therapy offers great hope for the treatment of genetic diseases/disorders and is currently being actively explored in airway diseases such as cystic fibrosis. Thus, such approaches can be considered for a potential permanent cure of airway epithelial defects of job syndrome. Finally, Job Syndrome is associated with a cluster of abnormalities in numerous organs including skin, bone, muscle, and connective tissues, therefore the study of tissue-specific abnormality will serve as a key to identifying the multidisciplinary and probably more efficient therapies for these affected individual organs.