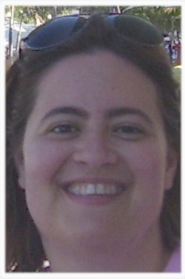
ImmunoTools *special* Award 2016



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Biomarkers of inflammation and impaired immunity in Cystic Fibrosis Related Diabetes (CFRD)

Cystic Fibrosis is an autosomal recessive disease caused by mutations in the CFTR gene. *Cystic fibrosis related diabetes* is the leading cause of comorbidity in cystic fibrosis patients. Its prevalence is age-related and its incidence is rapidly increasing because of the extension of the life expectancy in CF patients. Excluding insulin, therapies are limited. Thus, CFRD has a significant public health impact on the quality of life of patients especially because it is correlated to a decline of lung function and FEV1.

CFRD is a complex disease in which the relative contribution of genetic and environmental factors remains unclear. CFRD-susceptibility genes have been recently identified *(Diabetes 2013, 62, 3627–3635)*. The airway epithelium acts as an anatomical barrier to or primary defense against infection. Furthermore, it acts as a key mediator of both innate and adaptive immune responses toward invading pathogens. TLRs mediate the recognition of and response to microbial infections and are highly expressed on immune cells and AECs. In the CF lung, TLRs expressed by AECs contribute to the airway immune response by regulating the expression and secretion of cytokines, chemokines, and antimicrobial peptides and through enhancing the expression of cell surface adhesion molecules *(Expert Opinion on therapeutic Targets, vol. 12, no. 12, pp. 1481–1495, 2008).*

Bone marrow derived cells such as monocytes, macrophages, neutrophils, and dendritic cells are constantly recruited to clear pulmonary pathogens but numerous studies have suggested an impairment of these cells in the context of the CF. Neutrophils from people with CF have been found to release more elastase and have defective phagocytic capacity. Inflammation and impaired immune system may lead to damage in the CF lung and other organs. Patients with CF who have chronic P. aeruginosa infection show a qualitative impairment of Tregs. Modulation of Tregs represents a novel strategy to rebalance T-cell responses, dampen inflammation, and improve outcomes for patients with infective CF lung disease.

Ziai et al. reported that patients with or without CFRD had increased glucose excursions when compared to healthy peers. Patients with CF have increased glucose fluctuations and hyperglycemia and that this may affect the clinical course of CF and lead to lymphocyte dysfunction *(Diabetes Res Clin Pract. 2014 Jul; 105(1):22-9.)*. T-helper 17 lymphocytes produce and secrete the pro-inflammatory cytokine IL-17. The Th17 pathway is involved in CF lung inflammation, β-cell destruction in type 1 diabetes and Th17 cells of patients with type 2 diabetes have increased production of IL-17 when compared to healthy peers. Vitamin D can affect inflammation in CF, diabetes and the differentiation of lymphocytes. There are potential roles of hyperglycemia on Th17 cells, Tregs and IL-17 as potential causes for accelerated lung function decline before CFRD and vitamin D may be a modulator intervening in the IL-17A pathway.

Cystic fibrosis related diabetes is coming from genetic predisposition, environmental factors, inflammatory damage or autoimmunity? To date, it is not clear whether the presence of an impaired immunity in CFRD is a cause or a consequence of the chronic inflammation occurring in CF patients. The studies here proposed are aimed at understanding the specific role of the innate immune system in humans, specifically focusing on the T cells and dendritic cells interplay in the pathogenesis of CFRD. We will also investigate key components of the molecular machinery associated with TLRs, TLRs-downstream effectors and consequent secretion of pro-inflammatory factors, such as cytokines and chemokines. The ImmunoTools selected products would be of great benefit to this project as they would be used to study T cells and dendritic cells interplay and cytokines levels in this context.

ImmunoTools *special* AWARD for **Anna Lisa Montemari**

includes 25 reagents

FITC - conjugated anti-human CD8, CD11a, CD19, CD20, CD40, CD45RA, CD86, ANNEXIN V

PE - conjugated anti-human CD1a, CD4, CD14, CD62L, CD80, IFNg, IL-6, TNFa

APC - conjugated anti-human CD3, CD11b, CD11c, CD16, CD25

recombinant human cytokines: GM-CSF, IL-4, IL-10, TNFa

DETAILS more AWARDS