Iannitti RG, Carvalho A, Cunha C, De Luca A, Giovannini G, Casagrande A, Zelante T, Vacca C, Fallarino F, Puccetti P, Massi-Benedetti C, Defilippi G, Russo M, Porcaro L, Colombo C, Ratclif L, De Benedictis FM, Romani L. (2013). Th17/Treg Imbalance in Murine Cystic Fibrosis is Linked to indoleamine 2,3-dioxygenase Deficiency but Corrected by Kynurenines. Am J Respir Crit Care Med. 187:609.

RATIONALE:

Mutations in the cystic fibrosis (CF) transmembrane conductance regulator affect the innate epithelial immune function of the lung, resulting in exaggerated and ineffective airway inflammation that fails to eradicate pathogenic fungi. The appreciation of whether such fungi are primarily responsible for or a consequence of ineffective airway inflammation is important for future therapeutics development.

OBJECTIVES:

To characterize the impact of the tryptophan/kynurenine pathway on pathogenic airway inflammation preventing effective fungal clearance in CF.

METHODS:

We studied the expression of indoleamine 2,3-dioxygenase (IDO), the first enzyme in the kynurenine pathway of tryptophan degradation, in human and murine CF, the impact of IDO on lung inflammation and immunity in murine CF, and the potential role of tryptophan catabolism in pathogenesis and therapy of fungus-associated lung inflammation.

MEASUREMENTS AND MAIN RESULTS:

IDO was defective in murine and human CF. Genetic and transcriptional regulatory mechanisms contributed to dysfunctional IDO activity that, in turn, correlated with imbalanced Th17/Treg-cell responses to Aspergillus fumigatus in murine CF. Treatments enhancing IDO function or preventing pathogenic Th17-cell activation restored protective immunity to the fungus and improved lung inflammation in murine CF.

CONCLUSIONS:

This study provides a link between tryptophan catabolism and lung immune homeostasis in murine CF, representing a proof-of-concept that targeting pathogenic inflammation via IDO-mimetic drugs may benefit patients with CF.