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**RESEARCH HIGHLIGHT**

# Th17/Treg imbalance in murine cystic fibrosis and IDO deficiency

Flaminia Malvezzi-Campeggi

Fondazione per la Ricerca sulla Fibrosi Cistica, Ospedale Maggiore, Piazzale Stefani 1, Verona, Italy.
Email **fmalvezzich@gmail.com**

This study identifies a novel pathogenic mechanism that may contribute to Cystic Fibrosis (CF) lung disease, providing indications for immunogenic screening of IDO (indoleamine 2,3-dioxigenase) and kynurenine levels as biomarkers that reflect CF pathophysiology. It also suggests new therapeutics in CF lung diseases.

**Keywords**: Cystic Fibrosis, IDO, Th17, Treg

Cystic fibrosis (CF) is an autosomal recessive genetic disorder caused by a mutation in the gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR). This protein is required to regulate the components of sweat, digestive fluids, and mucus. CFTR regulates the movement of chloride and sodium ions across epithelial membranes, therefore patients suffering from CF are characterized by abnormal transport of chloride and sodium across an epithelium which leads to thick, viscous secretions. Difficulty when breathing is the most serious symptom and results from frequent lung infections that are treated with antibiotics and other medications.

The respiratory tract of CF patients is colonized, in addiction to bacteria, by many fungi, although whether they are primarily responsible for, or a consequence of an ineffective airway inflammation, remain controversial and largely unsolved. The respiratory system in patients with CF is characterized by high concentrations of neutrophils and pro-inflammatory cytokines, including IL-17A, with reduced concentrations of anti-inflammatory factors.

Th17 lymphocytes are present in the airway sub-mucosa in CF patients, and they are presumed to account for the underlying inflammatory status in those patients. Th17 cells are in balance with regulatory T (Treg) cells through the activity of the IDO (indoleamine 2,3-dioxigenase), the rate limiting enzyme in tryptophan degradation along the kynurenine pathway.

Based on these premises, in a recent paper Iannitti and coworkers (Iannitti et al., 2013) studied whether and how hypoxia acts as an up-stream regulator of the Th17/Treg cell balance in CF and whether hypoxia is a drugable target in CF. Decreased tryptophan kynurenine metabolism, as a result of defective IDO, was causally linked to susceptibility to

*Aspergillus* infection and sensitization in murine CF, because of the generation of a Th17/Treg imbalance. Treatments with IDO agonists or prevention of Th17 cell activation restored antifungal protective immunity and improved lung inflammation and function, suggesting a therapeutic potential for IDO mimetic drugs in CF.

The study identifies a novel pathogenic mechanism that may contribute to CF lung disease, provides indications for immunogenic screening of IDO1 and kynurenine levels as biomarkers that reflect CF pathophysiology and suggests new therapeutics in CF lung diseases. Since the paper indicates that genetic and epigenetic mechanisms collude to impair IDO activity and promote Th17-dependent inflammatory pathology in CF, the authors conclude that the inability to handle respiratory fungal pathogens could be responsible for the state of chronic inflammation in CF.

**Reference**

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