Targeting pathogenic pathways leading to inflammatory Th17 responses in cystic fibrosis: from drug discovery to preclinical validation

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Background. In patients with Cystic Fibrosis (CF), the progressive decline of pulmonary function is due to a vicious cycle of airways infection and inflammation. Inflammation can be more damaging than the insult itself if uncontrolled, excessive, or prolonged. Although there is debate over whether inflammation in the CF lung is primary (i.e., caused by CFTR mutations) or secondary to chronic infection, inflammation remains the single most significant contributor to disease progression, and its control is crucial for improving patient outcomes. Building upon the results from our past projects–indicating how the application of a systems biology approach and new findings from the laboratory may translate into the development of new therapeutics and rationales for their use–we have proposed a preclinical evaluation study of anakinra, a recombinant, non-glycosylated version of human IL-1 receptor I antagonist (IL-1Ra) in CF. Since 2001, anakinra has proved to be efficacious in a broad spectrum of auto-inflammatory diseases with a remarkable record of safety.

Hypothesis and Objectives. 1. The relative contribution of different inflammasomes to fungal and bacterial infections and inflammation in CF mice. 2.The evaluation of the efficacy of anakinra in experimental and preclinical models of CF. 3. The definition of the molecular mechanisms underlying anakinra activity. 4. The screening of CF patients for IL-1Ra deficiency and the definition of anakinra-responsive signatures through microarray gene expression profiling.

Methods. The project included experimental and human studies consisting of: 1. fungal or bacterial infections in selected, genetically-modified mice treated with anakinra; 2. in vitro studies on ex-vivo purified immune and non-immune cells from mice and human bronchial epithelial cells (HBE) from CF and non-CF patients; 3. the screening of CF patients for IL-1RA deficiency and microarray gene expression profiling.

Results. While both contributing to pathogen clearance, NLRP3 more than NLRC4 contributed to pathogenic inflammatory responses in murine and human CF and correlated with lower levels of IL-1Ra production and reduced NLRC4 activation. Pathogenic NLRP3 activity in CF could be negatively regulated by IL-1Ra and this provided a proof-of-concept evidence that IL-1Ra may limit the pathological consequences of microbial colonization in CF. Genetic analysis supported the role of NLRC4 and IL-1Ra in determining the state of microbial colonization of CF patients.

Spin-off for research & clinical purposes. This study will provide the foundation for repurposing a drug approved for other indications for the treatment of CF.

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