PROJECT

Supervisor: _____ Nicola I. Lorè

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Title: Dissecting mucosal immunopathology in non-tuberculous mycobacterial and *Pseudomonas aeruginsa* lung infection

Curriculum: _____ Basic and Applied Immunology and Oncology

Link to the personal page of the University or relevant hospital site website: __https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/emerging-bacterial-pathogens/nicola-ivan-lore.html __ _____

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Chronic respiratory infections by opportunist pathogens particularly affects individuals with pre-existing lung conditions such as bronchiectasis, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF) (1,2,3). However, persistent airway infections caused by Nontuberculous Mycobacterium (NTMs) and *P. aeruginosa* remain significant challenges, due to their ability for resisting to antibiotic treatments (5,6,7). In this context type 1 and type 17 immunity may play a critical role in modulating the outcome of these infectious processes. Therefore, additional and innovative therapeutic strategies, such those targeting immunity, are required for people with chronic respiratory infections and diseases who fail to clear lung infections.

Rationale and hypothesis

Chronic respiratory diseases are characterized by significantly reduced lung function, increased rates of infection with pathogens such as NTMs and/or *P. aeruginosa*, and heightened inflammation. Co-infections with NTMs and *P. aeruginosa* are common, yet the synergistic immunopathological mechanisms driving these infections in severe lung diseases remain poorly understood. This gap in understanding limits our ability to develop targeted interventions against host response and to slow or prevent disease progression.

This project aims to investigate the distinct and co-pathogenic roles of NTMs and *P. aeruginosa* in chronic lung infection and related immunopathological responses using a multi-faceted approach.

Objectives and specific aims

We will employ chronic infection human bronchial epithelial cells, macrophages cell lines and in vivo model of chronic respiratory Co-infection (8,9). In addition, omics technologies, including dual bulk RNA sequencing and spatial transcriptomics (10), will be used to map inflammatory, pathological and microbial responses in cellular and in vivo models with unprecedented resolution. Thanks to this approach we will understand:

i) what are the immunological responses (among type 1 and type 17 immune responses) that can differently modulate bacterial recognition and inflammatory signalling using epithelial barrier and alveolar macrophages cell lines pretreated with key inflammatory cytokines (e.g. IL17A or IFNs).

ii) how co-infections and related immune responses may impairs host defense (bacterial burdens modulation) and exacerbate immunopathology (tissue damage, pro-fibrotic and remodelling processes) using mouse models of chronic respiratory diseases;

Expected outcomes

This work will elucidate how immune response to single pathogens can modulate the co-infection outcome with a particular attention on mechanisms driving chronic lung immunopathology associated to persistent infections, providing critical insights for the development of personalized therapies for these uncurable diseases.

Skills that the student should acquire (max. 600 characters including spaces):

- learning and generating scientific knowledge on immune response in the context of respiratory infections

- technical know-how on in vivo and ex vivo models

- methodological knowledge on immunological/molecular biology/microbiological techniques (E.g. Flow cytometry, Real Time and Luminex technology, RNAseq, scRNA-seq, tissue spatial transcriptomics)

- technical know-how on data analysis and how to work towards the result (R environment, Seurat package)

References (max. 15)

1) Van Braeckel E, et al (2024) Growing from common ground: nontuberculous mycobacteria and bronchiectasis. Eur Respir Rev.

2) Cutting GR. (2015) Cystic fibrosis genetics: from molecular understanding to clinical application. Nat Rev Genet

3) Loebinger MR et al; (2024) Patients at risk of nontuberculous mycobacterial pulmonary disease who need testing evaluated using a modified Delphi process by European experts. ERJ Open Res.

5) Roesch EA, Nichols DP, Chmiel JF. (2018) Inflammation in cystic fibrosis: An update. Pediatr Pulmonol 53: S30-S50.

6) Daley CL, et al. (2020) Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Eur Respir J 56.

7) Johansen MD, et al (2020) Non-tuberculous mycobacteria and the rise of Mycobacterium abscessus. Nat Rev Microbiol 18: 392-407.

8) Lorè NI, et al, (2022) The aminoglycoside-modifying enzyme Eis2 represents a new potential in vivo target for reducing antimicrobial drug resistance in Mycobacterium abscessus complex. Eur Respir J. 2022

9) Lorè NI, et al, (2016) IL-17A impairs host tolerance during airway chronic infection by Pseudomonas aeruginosa. Sci Rep. 2016 May

10) Di Marco F, et al. (2024) Dual spatial host-bacterial gene expression in Mycobacterium abscessus respiratory infections. Commun Biol.