PROJECT 2 (optional)

DoS: Daniela Maria Cirillo

Title: The role of the immune response in the pathogenesis of Non-Tubercular Mycobacteria Lung infection

Curriculum: Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page:
https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/emerging-bacterial-pathogens/daniela-maria-cirillo.html

Project description (*Number of characters*, *including spaces*: 2.000 - 3.000):

Nontuberculous mycobacterial (NTM) pulmonary disease has emerged as major threat to the health of individuals with cystic fibrosis (CF). *M. abscessus* (MA) is one of the most frequently isolated NTM in patients with CF[1]. Not all patients progress to severe disease, but for those progressing the treatment is provided for more the two years with at least three drugs to attempt to overcome the multidrug resistant nature of pathogen. Toxicity of treatment further contributes to severe life-long side effects[2].

Understanding the pathogenicity of the disease, and the interaction between virulent and attenuated clones and the host would lead to personalized treatment of patients with an increased risk of progressing to severe lung damage. Although some of the host and pathogen factors have been associated to the disease progression, the role of the immune response at the MA-lung interface in leading the progression of the disease has never been properly investigated for the absence of suitable animal models.

In the past two years we have generated and characterized a mouse model of chronic NTM infection[3]. This project aims to understanding the role of the immune response regarding host defense and immunopathology during MA lung infection, focusing on chronic inflammation induced by persistence of the pathogen (a key factor in determining the severity of the permanent lung damage). We will use different *in vitro/ex vivo* models of infection, and our murine model of long-term infection by MA in C57BL/6N mice to improve our understanding of the host-MA interaction. MA clinical isolates with different pathogenic features (virulence, clinical presentation and progression) will be used.

Through *in vivo* experiments we will determine inflammatory response (immune cellular recruitment, cytokines profiles and RNA bronchial epithelial profiles), tissue remodeling, and damage (macrophage phenotypes, collagen deposition, Matrix metalloproteinases) in C57BL/6N mice with lung disease due to different MA clones. These results will be validated in *in vitro/ex vivo* studies by investigating the host transcriptomic profile during host-MA interaction, and by assessing host-pathogen interactions using mutant strains expressing fluorescent tags (confocal microscopy). Cytotoxicity and the pro-inflammatory profiles will be also monitored (Luminex technology and bulk RNA sequencing approaches). This approach will allow us to determine the key pathogenic features

of MA by better understanding 1)the immune response induced by MA persistence *in vivo*, and 2)the host-MA interaction at cellular level in *in vitro/ex vivo* experiments.

This research proposal will elucidate the role of immune response in determining disease progression mediated by MA infection and persistence. A better understanding of immune mechanisms contrasting MA infection and persistence will allow us to unravel new therapeutic targets limiting lung disease progression during nontuberculous mycobacterial pulmonary disease.

Skills to be acquired by the student:

- scientific independence, critical thinking, problem solving
- learning and generating scientific knowledge on immune response in the context of respiratory infections
- technical know-how on in vivo and in vitro mouse model
- methodological knowledge on immunological/molecular biology/microbiological techniques (E.g. Flow cytometry, Real Time and Luminex technology, RNA-seq)
- technical know-how on data analysis and how to work towards the result

References (max. 3)

1) Tortoli E. et al ERJ 2017 PMID: 28705942
2) Daniel-Wayman S. et al AJRCCM 2018 PMID: 30428263
3) Riva C. et al Int J Mol Sci. 2020 Sep 9;21(18):6590.