A Model for Studying Mycobacterial Nutrient Uptake

Ionescu, Iris (School: Colegiul National Zinca Golescu)

Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains the deadliest infectious disease, responsible for approximately 1.25 million deaths and 10 million new cases in 2023. A major factor contributing to mycobacterial resilience is its highly impermeable outer membrane, which serves as a protective barrier against hostile environments, including antibiotics and immune responses. However, despite this protective "armor," mycobacteria must still acquire essential nutrients for survival. They achieve this through two distinct pathways: (I) the ESX-5 type VII secretion system (T7SS), used by pathogenic species, or (II) MspA porins, found in non-pathogenic species that allow general diffusion. Due to the difficulty of working with pathogenic mycobacteria, we aimed to establish a non-pathogenic model to study ESX-5's role in nutrient uptake. Using a non-pathogenic species engineered to express the ESX-5 system, we analyzed its membrane permeability and antibiotic resistance compared to control strains. Interestingly, we found that ESX-5 expression reduced membrane permeability, suggesting that this system contributes to a more restrictive cell envelope. To determine whether ESX-5 enables nutrient uptake in this new host, we attempted to delete the native nutrient uptake systems, the MspA porins, using CRISPR-Cas. This proved unsuccessful, likely due to the absence of ESX-5 substrates fulfilling a nutrient transport role. A genetic and structural analysis of known ESX-5 substrates identified potential substrate candidates based on published work. Future research will focus on introducing these substrates alongside ESX-5 to assess their impact on membrane permeability and nutrient uptake, providing deeper insight into the role of ESX in pathogenic mycobacteria.

Awards Won: