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DISSERTATION

"Impact of immune cell type on drug distribution in tuberculosis lesions"

by

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M.D./Ph.D. Program

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ICPH 1st floor TB-training room W140B.1

Abstract

Tuberculosis (TB) has plagued humankind since ancient times and, although it is now treatable with modern antibiotics, it remains a worldwide burden infecting up to one third of the world's population and is responsible for the deaths of over one million people every year. This is largely due to the inefficiency of anti-TB drug therapy which, even for the drug susceptible strains of TB, require a minimum 6 months treatment with multiple antibiotics. This inefficiency of TB treatment is largely due to the complex structural nature of the tuberculosis granuloma which provides numerous niche microenvironments in which the bacteria thrive, become dormant, and/or are protected from various antibiotics used to treat TB. In order to develop better ways to combine anti-TB drugs to target each and every niche where the bacteria reside within the host, it is necessary to take a closer look at how drugs interact with each individual cellular component of the TB granuloma. In the present work, we have examined and quantified the intracellular accumulation of anti-TB drugs within alveolar epithelial cells, lymphocytes, neutrophils, macrophages, and foamy macrophages in order to understand the in vivo spatial distribution of fluoroquinolones in TB lesions with respect to the various cellular components of the lesions. We have demonstrated that macrophages are primarily responsible for fluoroquinolone distribution which is further confirmed using a collaborative in vivo approach involving MALDI mass spectrometry imaging, H&E analysis, and mathematical modeling. We have further investigated drug uptake in macrophages and foamy macrophages using a panel of 19 anti-TB drugs and have determined that fluoroquinolones, but not any of the other 19 anti-TB drugs, show two-fold increased uptake in foamy macrophages compared to non-foamy macrophages. The mechanism for this fluoroquinolone specific differential uptake was investigated and demonstrated to be due to a decreased expression of multidrug resistance protein (MRP/ABCC) exporter proteins in foamy macrophages. In addition to the static role immune cells play in drug distribution, we have investigated neutrophils as a potential targeted drug delivery system based on their high rate of migration to the central avascular regions of some TB lesions. Using retrospective analysis of linezolid and tedizolid MALDI mass spectrometry images combined with prospective in vitro data of drug accumulation in neutrophils, we have proposed that neutrophils are responsible for the active delivery of tedizolid, but not linezolid, to avascular necrotic centers of pulmonary TB lesions. Further data emerging from the in vitro neutrophil drug accumulation analysis indicated that rifalazil would be an ideal drug candidate to test the hypothesis of neutrophil-mediated drug delivery to the necrotic center of TB lesions. Subsequent analysis of rifalazil distribution in 10 lesions from TB infected rabbits demonstrated a positive correlation between rifalazil penetration and neutrophilicity of caseum within necrotic TB lesions, confirming the Trojan horse hypothesis and forming the basis of future studies with increased sample size. The overall goal of this study is to develop, optimize, and validate in vitro assays that can aid further research and development of a more efficient, patient centered, anti-TB therapy that works in harmony with the natural immune system.