Chaperones and substrate specificity, type VII secretion systems reconnected

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2019

document version
Publisher's PDF, also known as Version of record

PhD research summary

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Mycobacterium tuberculosis, the causative agent of tuberculosis, annually kills ~1.5 million people and is considered as the most deadly bacterial pathogen worldwide. This pathogen is particularly successful in establishing long-term infections by manipulating the immune system and exploiting nutrient resources of the host. Although we do not fully understand how *M. tuberculosis* interacts with its host, secreted proteins play a crucial role in this process. Protein secretion by mycobacteria is complicated by the presence of a highly unusual and complex cell envelope. Recently, it has been shown that many of these proteins are exported via a novel protein transport pathway, called type VII secretion (T7S). Strikingly, *M. tuberculosis* contains five different T7S systems, underscoring the importance of the secretion pathway for this pathogen. Elucidating T7S is essential to understand the success of *M. tuberculosis* as a pathogen, and to identify targets for novel drug- and vaccine development. However, T7S is completely different from any other known secretion pathway and its functional mechanism is largely unknown. During my PhD, I have focused on studying the mechanism of the substrate recognition in the T7S systems. For this, I have used molecular, biochemical and proteomic techniques. In addition, I have investigated which signatures determine system specificity for each substrate group, and used this information to successfully manipulate rerouting specific substrates from one T7S system to another. Substrate rerouting will be instrumental in studying the individual role of substrates in virulence, and could help to improve the current live vaccine strain through modulation of the antigen repertoire.