

Microbial biofilms: Molecular mechanisms to potential therapeutics

P. Lynne Howell

Program in Molecular Medicine, The Hospital for Sick Children, Toronto, ON, M5G 0A4, Canada

Microbial biofilm infections are a significant medical problem as treatment usually fails to irradiate the microbes and typically results in chronic and often life-threatening conditions for the patient. Biofilms are multicellular microbial communities surrounded by a self-produced protective coating. Exopolysaccharides are a key component of this coating in many microbial species where they are involved in initial colonization as adhesins, provide three-dimensional structure to the biofilm, and offer protection against antimicrobials and host defense mechanisms. Our research to understand the molecular mechanisms of how the exopolysaccharides Pel and Psl from *Pseudomonas aeruginosa* and galactosaminogalactan (GAG) from the fungus *Aspergillus fumigatus* are synthesized led to the identification of genes encoding putative glycoside hydrolases within the biosynthetic machinery. Our structure-function analyses revealed that the recombinant enzymes can hydrolyze their respective polysaccharides and that each protein has a (β/α)₈ TIM-barrel fold. Further, we have found that exogenous addition of low nanomolar concentrations of these enzymes are sufficient abrogate biofilm formation and disperse mature biofilms from lab, clinical, and environmental isolates. The enzymes enhance neutrophil killing and potentiate the activity of antimicrobials. The enzymes are non-cytotoxic and can protect A549 pulmonary epithelial cells from *A. fumigatus*-induced cell damage for up to 24 hours. Preliminary animal studies show that intratracheal administration of Sph3 is well tolerated and reduces pulmonary fungal burden in a neutropenic mouse model of invasive aspergillosis. Our current understanding of the molecular mechanisms used in exopolysaccharide production as well as our progress towards the development of novel antimicrobials will be discussed.