Virus-Mimicking Polymer Molecular Brushes Are Potent Antibiotics with High Selectivity

Hongjun Liang, Ph.D., Associate Professor
Department of Cell Physiology and Molecular Biophysics
Texas Tech University Health Sciences Center

Antibiotic resistance has become one of the greatest healthcare challenges. Our society faces an urgent need to develop new generations of antibiotics that can thwart bacterial responses. Antimicrobial (host-defense) peptides (AMPs) and synthetic mimics of AMPs (SMAMPs) emerge as promising candidates. Their cationic charge and amphiphilicity are identified as the two key antimicrobial traits that help them disrupt bacterial membranes *via* a combination of hydrophobic and charge interactions. Because this action works nonspecifically on membrane lipids, it often enlists unbearable cost for bacteria to develop resistance. However, a central dichotomy persists in that the hydrophobicity needed for their antimicrobial performance also causes their toxicity to mammalian cells. Numerous chemical variations have been tested in search of a delicate yet unquantified balance between amphiphilicity and electropositivity. I will discuss here a different approach to develop membrane-active antibiotic by designing well-defined polymer molecular brushes (PMBs) that mimic the structural characteristics of bacteria-invading viruses. Our preliminary data based on PMBs with hydrophilic polymer brushes reveal that: (1) amphiphilicity is not a required trait – hydrophilic PMBs can be designed to have potent antibiotic performance as well with negligible hemolytic activity; (2) the nanoscale architecture of PMBs defines their double selectivity, not molecular weight *per se*; (3) PMBs are far more powerful antibiotics than individual linear-chain polymers that make up the PMBs; and (4) nanostructured PMBs induce topological changes of membranes by forming membrane pores that unlikely fit in with any known models of AMP action. These findings expand existing wisdom and suggest that the spatially-defined, multivalent interactions inherent to the nanostructured PMBs is of great significance for the development of new membrane-active antibiotics.