NANOHOUR

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3:00 PM
Beckman Institute - Room 3269

Polyelectrolyte physics and cystic fibrosis

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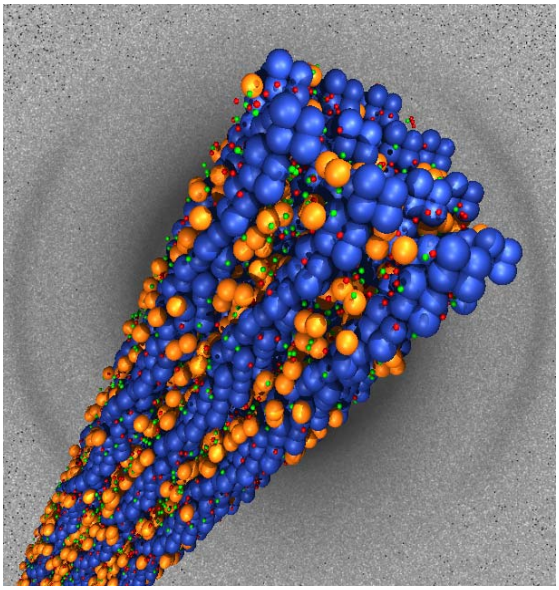

The accumulation of viscous mucus in pulmonary airways is the primary cause of long-term bacterial infections, respiratory failure, and eventually death in cystic fibrosis (CF). The inflammatory response to infections in the airways leads to the pathological release of charged cytoskeletal proteins, DNA and as well as other polyelectrolytes. For example, in addition to the anionic mucin comprising normal mucus, CF mucus contains highly anionic polyelectrolytes such as extracellular filaments from bacteria, as well as F-actin and DNA released from lysed inflammatory cells. The concentration of DNA in CF sputum can be as high as 20mg/ml, and comprises 4-10% of the dry weight of the sputum. Likewise, reported F-actin concentrations in sputum are in the 0.1-5mg/ml range. These adventitious polyelectrolytes can cause the electrostatic assembly of large aggregates stabilized by cationic ligands in CF mucus. It has been suggested that endogenous cationic antibacterial proteins constitute a significant fraction of the ligands holding these polyelectrolyte aggregates together. This binding leads to the sequestration and inactivation of these antibacterial agents, and therefore contribute to long-term infections in CF. Examples of such cationic ligands include antibacterial proteins such as lysozyme, lactoferrin, ß-defensin, and LL-37, as well as antibiotics currently used in CF treatment such as the aminoglycosides. We have studied electrostatic interactions between antimicrobials and airway polyelectrolytes from the perspective of soft condensed matter physics. By combining synchrotron small-angle x-ray scattering, molecular dynamics simulations, and genetic engineering, we show how antimicrobials can be liberated from polyelectrolyte complexes using the prototypical actin-lysozyme system. We confirm the existence of actin-lysozyme complexes in CF sputum using x-ray microscopy and demonstrate that, at a wide range of salt conditions, charge-reduced lysozyme is no longer sequestered in ordered complexes, while retaining its bacterial killing activity.

Coffee and cookies will be served.
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