Improving gene therapy vector delivery in the lung by removing cell surface glyocalyx mucins

The lungs are coated with a dual layer of secreted and tethered mucins produced by epithelial cells allowing them to be resilient against pathogens, toxins, and microorganisms frequently inhaled by the air. In patients with cystic fibrosis, the mucus is hyperconcentrated causing ineffective mucus clearance by cilia beating or coughing, creating a breeding ground for microbes and pathogens. To deliver gene therapy vectors to cystic fibrosis patients, the drugs must pass through the mucus and cell-surface glyocalyx which is difficult due to the thick mucus. Therefore, the ability of the mucin-specific protease, StcE, to cleave secreted and tethered mucins is studied to allow gene therapy vectors to reach the cell surface. The presence of glyocalyx proteins both before and after StcE treatment was visualized using various fluorescent dyes via confocal microscopy. These images indicate a decrease in mucin proteins and the glyocalyx after StcE treatment, highlighting StcE’s ability as a mucin-specific protease. StcE’s effectiveness in cleaving mucin proteins, decreasing cell exclusion height, is visualized via AAV2 and coronavirus infection. Increased infection rates for AAV-2 and coronavirus (NL63) were seen after StcE treatment indicating the ability of viral vectors to more readily access the cell surface because of the decreased exclusion height. Collectively, these observations show promise for effectively cleaving the glyocalyx allowing for gene therapy drug delivery and future studies in building up glyocalyx proteins to create a denser periciliary layer to exclude smaller vectors and potentially limit viral infections.