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Title:

GLYCOSAMINOGLYCANS ARE DIFFERENTIALLY INVOLVED IN BACTERIAL BINDING TO HEALTHY AND CYSTIC FIBROSIS LUNG CELLS

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What was your research question?

Our purpose in this work was to evaluate and identify the differences in cell surface saccharide (sugar) molecules called glycosaminoglycans between healthy and cystic fibrosis (CF) cellular models and to determine their involvement in the adhesion of some of the main pathogens causing recurrent infections in CF.

Why is this important?

The main cause of morbidity and mortality in people with CF is lung damage resulting from an inflammatory over-response triggered by recurrent infections in the respiratory tract. The increase of antibiotic resistance pathogens necessitates the urgency to find new anti-infective therapies. The first critical step for minimizing infection is understanding the pathogen's adhesion to host tissue. Knowing the underlying molecular mechanisms of this interaction might enable the design of strategies that interfere with bacterial adhesion. Glycosaminoglycans, which are found in all mammalian cells, display a wide variety of normal and disease-related functions, like acting as mediators in many infectious processes.

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What did you do?

A comparative study was performed to assess the level of important genes encoding cell surface glycosaminoglycans in two cell lines, which were previously accepted as models of normal lung and CF epithelium (cellular models). The role that glycosaminoglycans play in the adhesion of pathogenic bacteria commonly involved in CF, e.g. *Pseudomonas aeruginosa*, was analyzed by reducing their levels on the cell surface via degradation with lyases before proceeding to adhesion assays. Furthermore, examples of different types of glycosaminoglycans (that differ in their chemical structure) are heparan or chondroitin sulfate and to investigate their role, binding competition experiments were performed in the presence of different concentrations of the glycosaminoglycans.

What did you find?

There were some differences observed in the levels of important genes encoding glycosaminoglycans structure between both cellular models, mainly affecting their sulfation pattern, which may alter their interaction with microorganisms. The removal of glycosaminoglycans from the cell surface resulted in a decrease in adherence of all typical CF pathogens to both cellular models, except non-mucoid *Pseudomonas aeruginosa* which appeared to use other receptors for attachment. However, glycosaminoglycans effects on the adhesion of most of the bacteria varied depending on the cellular model used, probably due to their structural differences. Heparan sulfate appears to be the most important glycosaminoglycans involved in bacterial binding .

What does this mean and reasons for caution?

Understanding molecular details that determine the relationship between bacteria and their surface receptors on host cells is essential in developing new therapeutic treatments. We demonstrated the relevance of glycosaminoglycans, specifically their sulfation pattern, in the adherence of some of the most common bacterial pathogens found in CF. Mucoid *Pseudomonas aeruginosa* causes a great percentage of chronic infections and differences in the phenotypes of *Pseudomonas aeruginosa* were also observed, with glycosaminoglycans offering a more clear determinant in mucoid than non-mucoid phenotype adhesion. Although all these results have been proven with both bacterial strains typified as clinical isolates, they can vary when tested in animal models.

What's next?

This CF cellular model could be used in further studies focused on interfering with glycosaminoglycans pathogen interactions. For this, diverse strategies may be employed such as the use of specific antibodies or different molecules that mimics glycosaminoglycans receptors. The conclusions drawn from these results should also be tested in vivo.

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