The Effect of Galactosialidosis on Collagen Remodeling

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is characterized by emphysematous destruction of lung parenchyma and small airways obstruction/striction. The most common causes for COPD are smoking exposure or Alpha1-Antitrypsin deficiency (AAT). AAT deficiency is a genetic mutation that results in decreased production and normal function of the protein. Mice deficient in AAT develop lung emphysema due to proteolytic destruction of the alveolar lung tissue. In comparison to smoking-associated emphysematous destruction of the lung which causes centriacinar emphysema, AAT deficiency results in paracrine emphysematous type of the Alveoli. It was recently observed in a 37 year old male Galactosialidosis patient from St Paul’s Hospital. Aim: To understand how the CTSA mutation in Galactosialidosis affects the collagen contraction.

Introduction

Chronic obstructive pulmonary disease (COPD) encomasses emphysematous destruction of lung parenchyma and small airways obstruction/striction. The most common causes for COPD are smoking exposure or Alpha1-Antitrypsin deficiency (AAT). AAT deficiency is a genetic mutation that results in decreased production and normal function of the protein. Mice deficient in AAT develop lung emphysema due to proteolytic destruction of the alveolar lung tissue. In comparison to smoking-associated emphysematous destruction of the lung which causes centriacinar emphysema, AAT deficiency results in paracrine emphysematous type of the Alveoli. It was recently observed in a 37 year old male Galactosialidosis patient from St Paul’s Hospital. Aim: To understand how the CTSA mutation in Galactosialidosis affects the collagen contraction.

Hypothesis & Aims

Fibroblasts from our Galactosialidosis patient will have defective collagen I production and contraction compared to those of normal males. Aim 1: Compare collagen I gel contraction abilities between Galactosialidosis affected fibroblasts in comparison to control donors. Aim 2: Observe the differences in orientation of collagen fibers derived from collagen I gels remodeled from our donor and control males.

Results

Average contraction of fibrillar collagen from normal parenchymal fibroblasts in comparison to normal parenchymal fibroblasts

Figure 3. Donor Cohort: Donor 1, Donor 2, Donor 3

Table 1: Donor Cohort

<table>
<thead>
<tr>
<th>Donor</th>
<th>Age</th>
<th>Sex</th>
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<tbody>
<tr>
<td>Normal</td>
<td>25</td>
<td>M</td>
</tr>
<tr>
<td>Normal</td>
<td>20</td>
<td>M</td>
</tr>
<tr>
<td>Galactosialosis</td>
<td>37</td>
<td>M</td>
</tr>
</tbody>
</table>

Table 2: Collagen I gel contraction of normal and Galactosialidosis derived fibroblasts

<table>
<thead>
<tr>
<th>Collagen I Gel Contraction</th>
<th>Parenchymal Fibroblasts</th>
<th>Airway Fibroblasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor 1</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>Donor 2</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Donor 3</td>
<td>70%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Figure 4. Comparison of fibrillar collagen between normal and Galactosialidosis derived Parenchymal Fibroblasts

Figure 5. Comparison of fibrillar collagen between normal and Galactosialosis derived Airway Fibroblasts

Comparison of fibrillar collagen between normal and Galactosialidosis derived Parenchymal Fibroblasts

Figure 6. Comparison of fibrillar collagen between normal and Galactosialidosis derived Airway Fibroblasts

Future Aims

The lab aims to perform western blots on the gels to determine if the contractile machinery of fibroblasts is defective in our Galactosialidosis patient and to see if elastin production is also defective in lung derived fibroblasts.

Conclusion

The significance of defective collagen contraction and remodeling by fibroblasts obtained from Galactosialidosis patients leads to defective collagen homeostasis.

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References

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