Effect of Group 1 CD1-restricted T cells on Atherosclerosis

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* The study resulting in this presentation was assisted by a grant from the Undergraduate Research Grant Program which is administered by Northwestern University’s Office of the Provost. However, the conclusions, opinions, and other statements in this presentation are the author’s and not necessarily those of the sponsoring institution.

INTRODUCTION

Approximately 1 in 3 deaths in the US is caused by cardiovascular diseases like atherosclerosis. Atherosclerosis occurs through excessive cholesterol deposition (hyperlipidemia) along the inner layer of the artery called the intima, resulting in plaque formation that blocks arterial blood flow and leading to heart attacks and strokes. It has recently been recognized that inflammation plays an important role in plaque formation.

CD1-restricted T cells are a unique subset of T cells that respond to self and foreign lipid antigens presented by group 1 CD1d (CD1a, -b, -c) and group 2 CD1 (CD1-d) antigen presenting molecules (i.e. macrophages and dendritic cells). Group 2 CD1d molecules are known to associate with invariant NKT cells and induce apoptosis and necrosis in plaques. Numerous studies have shown that NKT cells play a pathogenic role in atherosclerosis using cytokines (IFN-γ, IL-4, IL-17, etc.) that activate other immune cells (e.g. T cells, B cells, and NK cells).

Group 1 CD1 molecules present lipid antigens to a diverse set of T cells with different types of receptors that recognizes lipid antigens specifically, and result in slow and long lasting adaptive-like immune response. Nothing is known about the role of group 1 CD1-restricted T cells in atherosclerosis and hyperlipidemia. This discrepancy is due to lack of an appropriate animal model to conduct such experiments. Mice, commonly used animal model for immunological studies, express only group 2 CD1d, not group 1 CD1 molecules.

This study looks at the unknown role of lipid antigen presenting molecules, specifically CD1b and CD1c subset molecules, on atherosclerotic plaque formation around intima of aortas in new experiments. Mice, commonly used animal model for such experiments. Mice, commonly used animal model for immunological studies, express only group 2 CD1d, not group 1 CD1 molecules.

RESULTS

The results of this study indicate that hCD1Tg/CD1dko/LDLrko group had the highest plaque area with an average of 1.26x10^5 um^2. Compared to the control mouse strain (LDLrko) with an average plaque area of 9.20x10^4 um^2, both hCD1Tg/LDLrko and hCD1Tg/HJ1Tg/LDLrko mice had lower average plaque areas (8.16x10^5 and 5.55x10^5 um^2, respectively).

One-way ANOVA and Turkey post-hoc statistical tests were performed. Plaque comparison by sex was also performed. Statistical significance between sexes are also shown. * p<0.05.

FUTURE RESEARCH & SIGNIFICANCE

Future research with an extended high fat diet period (16-18 weeks) can determine whether HJ T cell receptors are activated in hyperlipidemic mice. Clinical uses of this research may include manipulating group 1 CD1-restricted T cells to control heart plaque formation and, possibly, preventing atherosclerosis and heart attacks.

Figure 1. Oil red O-stained sections of aortic root plaque areas from hCD1Tg/HJ1Tg/LDLrko and LDLrko mice.

Table 1. Average plaque areas(um^2) from each group is listed along with the standard deviations.

<table>
<thead>
<tr>
<th>Treatment between columns</th>
<th>SS</th>
<th>DF</th>
<th>MS</th>
<th>F (DFn, DFd)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HJ1Tg vs. LDLrko</td>
<td>1.08x10^12</td>
<td>3</td>
<td>3.62x10^11</td>
<td>F (3, 20) = 7.173</td>
<td>P=0.0019</td>
</tr>
<tr>
<td>CD1dko vs. LDLrko</td>
<td>2.09x10^12</td>
<td>23</td>
<td>9.50x10^10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. One-way ANOVA table outlines sum of squares (SS) between groups and within groups, the degrees of freedom (DF), and mean square (MS). The final results, including the F ratio and P-value, are also stated. P<0.05.

Table 3. Sidak’s multiple comparisons test was performed to determine the statistical significance between groups. The figure also includes the mean difference, 95% confidence interval of the difference, and statistical significance. *p<0.05; **p<0.001.

Table 4. Average plaque area and standard deviation for each sex in the LDLrko, hCD1Tg/LDLrko, and hCD1Tg/HJ1Tg/LDLrko mice.

<table>
<thead>
<tr>
<th>Treatment between columns</th>
<th>LDLrko</th>
<th>hCD1Tg/LDLrko</th>
<th>hCD1Tg/HJ1Tg/LDLrko</th>
<th>hCD1Tg/CD1dko/LDLrko</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>8.48x10^5</td>
<td>1.02x10^6</td>
<td>9.78x10^5</td>
<td>5.48x10^5</td>
</tr>
<tr>
<td>Females</td>
<td>1.28x10^5</td>
<td>2.12x10^5</td>
<td>2.40x10^5</td>
<td>1.01x10^5</td>
</tr>
</tbody>
</table>

Table 5. T-test results for males and females in only hCD1Tg/LDLrko group showed statistical significance. *p<0.05.

SUMMARY

- Significant unexpected difference in plaque areas between the control mice (LDLrko) and mice with CD1b-restricted T cells (hCD1Tg/HJ1Tg/LDLrko).
- Overexpressing CD1b-restricted T cells (HJ1Tg) decreased plaque count. This refutes the initial hypothesis that CD1b-restricted T cells (HJ1Tg) would increase plaque area.
- Possibly due to inactivation of HJ T cells.
- Significant difference between control (LDLrko) and hCD1Tg/LDLrko mice.
- hCD1Tg mice do not harbor CD1b and CD1c-restricted T cells.
- hCD1Tg/LDLrko has lower plaque area than hCD1Tg/CD1dko/LDLrko mice.
- CD1d-restricted T cells (i.e. NKT cells) may have an inhibitory effect on CD1c and CD1b-restricted T cell activation or function.
- Unclear whether males usually have a greater plaque formation than females.

ACKNOWLEDGEMENTS

Dr. Chyung-Ru Wang, PhD
Dr. Sreya Bagchi, PhD
Dr. Lavanya Visvabharathy, PhD
Ying He (Lab Manager)