Deciphering the Interactions between Feline Mesenchymal Stem Cells and CD8+ T Cells In Vitro

Ash Sundaram, Naomi J. Walker, Dori L. Borjesson, Integrative Pathobiology

Introduction

- Mesenchymal stem cells (MSCs) are multipotent stem cells with the ability to modulate both innate and adaptive immune responses. Hence, they are a promising therapy for immune mediated and inflammatory disorders.
- Feline chronic gingivostomatitis (FCGS) is a severe and debilitating immune mediated oral disease of cats that is often refractory to treatment.
- Recently, we found that MSC administration results in complete clinical cure in ~70% of cats with FCGS. However, the mechanisms by which MSCs heal tissues in immune-mediated diseases are poorly understood.

Figure 1: A. Feline Chronic Gingivostomatitis
B. Clinical Response to MSC Therapy in Cats

Significance

- FCGS can serve as a spontaneous disease model for immune mediated oral mucosal diseases in humans including:
  - oral lichen planus
  - pemphigus
  - apthous stomatitis
- Such diseases in cats & humans are both characterized by:
  - T cell activation and tissue destruction
  - increased percentages of CD8+ T cells and effector T cells in both blood and oral tissues

Goal

- Determine the impact of MSC priming/reprogramming of CD8+ T cells on proliferation of activated T Cells
- Determine if MSC priming of CD8+ T cells is mediated by cell-to-cell contact or by soluble mediators

Experiment

Co-incubate feline MSC and activated CD8+ T Cells with contact and without contact [separated by a transwell]

Remove the above primed CD8+ T Cells and co-incubate with activated T cells

Determine lymphocyte proliferation by flow cytometry

Results

Flow cytometric analysis of functional assays

<table>
<thead>
<tr>
<th>Activated T Cells co-incubated with CD8+ T Cells not primed by MSCs</th>
<th>Activated T Cells co-incubated with CD8+ T Cells primed by MSCs in Contact</th>
<th>Activated T Cells co-incubated with CD8+ T Cells primed by MSCs in Transwell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation: 69.8 %</td>
<td>Proliferation: 17.2 %</td>
<td>Proliferation: 63.6 %</td>
</tr>
</tbody>
</table>

Results (cont)

There is a contact-dependent difference in how CD8+ T cells respond to MSCs:
- After direct contact with MSCs, CD8+ T cells inhibit the proliferation of activated T cells.
- In the absence of direct contact, CD8+ T cells did not inhibit the proliferation of activated CD4+ T cells.
- Findings suggest 2 mechanisms by which MSCs prime CD8+ T cells

Conclusion

- Determine the immunomodulatory cytokines that may regulate MSC-CD8+ T cell priming.
- Block secreted cytokines and/or cell surface receptors to determine which may be responsible for modulating MSC-CD8+ T cell interactions.

Future Work

- Determine the immunomodulatory cytokines that may regulate MSC-CD8+ T cell priming.
- Block secreted cytokines and/or cell surface receptors to determine which may be responsible for modulating MSC-CD8+ T cell interactions.

References

2. Glenn JD, Whartenby KA. Mesenchymal stem cells: Emerging mechanism of immunomodulation and therapy. World J Stem Cells 2014; 6(5); 526-539.
3. Carrade DD, Borjesson DL. Immunomodulation by mesenchymal stem cells in veterinary species. Comp Med 2013; 63(3); 201-217.
5. Chen TT, Verstraete FJM. Therapeutic efficacy of fresh, autologous mesenchymal stem cells for severe refractory gingivostomatitis in cats. Stem Cells in Translational Medicine. Jan 1, 2016; 5 (1)