Developmental composition and function of IgA-secreting cells in the lamina propria

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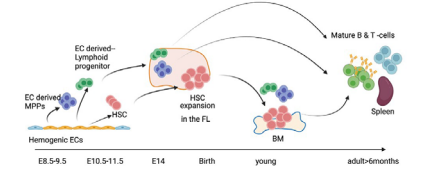
INTRODUCTION

While recent progress in developmental immunology has updated our understanding of the differentiation pathways of tissue resident immune cells, the developmental origins of IgA-secreting cells remain unclear.

Poly-reactive IgA is a subset of gut IgA that preferentially coats microbiota and prevents their invasion. Although it has recently been reported that IgA+ B-cells are derived from B-1b and B-2 cells, their ultimate origin has not been clarified because our lineage tracing data showed that B-1b and B-2 cells are derived from both endothelial cells (EC) and hematopoietic stem cells (HSC).



Our lineage tracing data also demonstrated that lamina propria (LP) IgA-secreting cells are mostly derived from endothelial cells. Our aim is to elucidate the origins of IgA-secreting cells and their functional differences based on their origins.

AIM

To investigate the progenitor cells of IgA-secreting cells in the LP from EC and HSC, we compared the IgA engraftment capacity of fetal and adult B-progenitors through transplantation studies.

METHODS

We transplanted 40K pro-B cells, derived from embryonic (E) 15.5 fetal liver (FL) or adult bone marrow (BM), into sublethally irradiated immunodeficient NOD/SCID/IL2rγ-/- (NSG) mice. Additionally, we transplanted 10K multipotent progenitor cells (MPPs) derived from E16.5 FL into NSG mice.

To assess IgA engraftment in LP, we conducted flow cytometry analysis, ELISA, and immunohistochemistry at several time points after transplantation.

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REFERENCES

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RESULTS

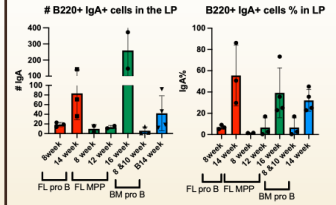


Figure 1: Engraftment of IgA from different progenitors evaluated by flow cytometry

FL pro-B cells: E15.5, FL MPPs: E16.5, BM pro-B cells:1-year-old mice

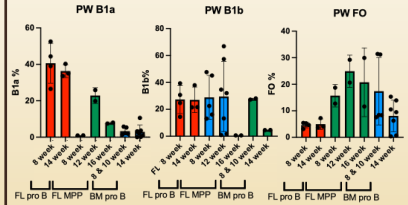


Figure 2: Engraftment of B-1a, B1-b, and FO B cells from different progenitors evaluated by flow cytometry

FL pro-B cells: E15.5, FL MPPs: E16.5, BM pro-B cells: 1-year-old mice

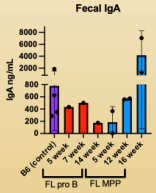


Figure 3: Concentrations of fecal IgA evaluated by ELISA

FL pro-B cells: E15.5, FL MPPs: E16.5

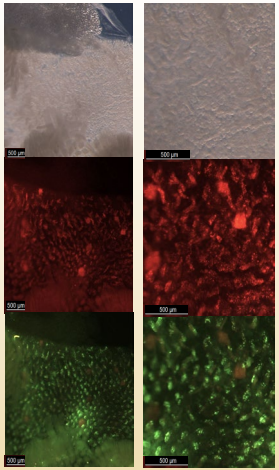
FL pro-B cells repopulated IgA⁺ cells at 7.0% and 55.5%, while BM pro-B cells repopulated at 6.7% and 39.2% at 8 weeks and 14 weeks, respectively, showing an increase in the engraftment of IgA⁺ cells over time (Fig. 1).

Transplantation of FL MPPs resulted in an increased number of IgA⁺ cells from 8 to 16 weeks (Fig. 1).
E16.5 FL MPP repopulated more B-1b and FP B cells than B-1a cells, indicating that E16.5 FL MPP contains more HSC-derived progenitors (Fig. 2).

In MPP-transplanted mice that successfully developed IgA-secreting cells, fecal IgA concentration gradually increased from weeks 5 to 16 (Fig. 3).

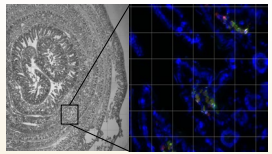
In pro-B cell-transplanted mice that successfully developed IgA-secreting cells, fecal IgA concentration peaked at week 7 (Fig. 3).

Picture 1

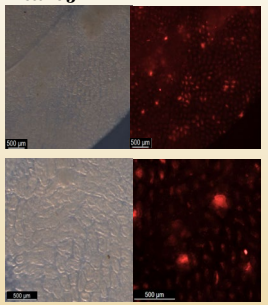


Whole-mount staining (Pic. 1) of the small intestine from MPP-transplanted mice at post-transplant week 16.
Green: IgA, Red: Tomato-positive donor cells

Picture 2



Picture 3



Frozen section (Pic. 2) and whole-mount staining (Pic. 3) of the small intestine from pro-B cell- transplanted animal at post-transplant week 14.
Green: IgA, Red: Tomato-positive donor cells, Blue: DAPI

CONCLUSION

Both fetal and adult pro-B cells showed similar IgA engraftment capabilities.

MPPs have a higher potential for CD45+ engraftment in the gut, but IgA engraftment percentages were at the same level. They may require at least 16 weeks to develop into IgA⁺ cells.
E16.5 FL MPPs have a longer engraftment capacity than we expected.

For future studies, we will transplant MPPs from E14.5 FL, from which the endothelial progenitors (EPs) dominantly produce blood cells, to investigate differences in the engraftment potential of IgA⁺ cells from EPs and HSCs.

To investigate possible functional differences among IgA+ secreting cells from different origins, we plan to introduce *C. rodentium infection* in mice reconstituted with two distinct origins of progenitors to evaluate functional differences.