Antigen archiving by lymphatic endothelial cells promotes secondary CD8+ T cell memory response during an unrelated infection

Thu Doan[1,3], Johnathon Schafer[1], Erin Lucas[1,2,3] and Beth A. Jirón Tamburini[1,2,3]

[1]University of Colorado Anschutz Medical Campus, School of Medicine, Department of Medicine: Division of Gastroenterology and Hepatology, Aurora, Colorado

[2]University of Colorado Anschutz Medical Campus, School of Medicine: Department of Immunology and Microbiology, Aurora, Colorado.

[3]Immunology Graduate Program, University of Colorado School of Medicine.

Abstract

Numerous studies have shown viral antigens can persist in lymph nodes after resolution of the infection. We showed that lymphatic endothelial cells (LECs), which comprise the lymphatic vasculature necessary for antigen drainage from the tissue, is the predominant cell type required for the persistence of antigen within the lymph node. We termed this process antigen archiving due the ability LECs to actively archive antigens to which an immune response has occurred. This process involves antigen acquisition, retention and exchange of the antigen between LECs and dendritic cells (DC), resulting in presentation of the archived antigens to CD8+ memory T cells and improving effector function. In more recent data, we demonstrated that LEC death causes the release of archived antigens during LN contraction. The objective of this study was to determine if during a second unrelated infection whether LEC death would occur and cause archived antigens would be released. As expected, we found that a second and unrelated viral infection causes LEC death within two to three weeks following infection. Within the same time frame that we observed LEC death we observed a significant increase in archived antigen-specific endogenous memory T cells. This increase only occurred in mice that received an unrelated viral infection and not in those mice that did not receive the unrelated viral infection. In conclusion, archived antigen release during a secondary unrelated infection potentially boosts the archived antigen specific memory CD8 T cell population. Understanding the mechanism of antigen release during multiple infections could ultimately lead to better strategies for vaccination and improve our understanding of how LECs influence immunity.

Fig. 1. Vaccine antigens persist on lymphatic endothelial cells in the lymph nodes.

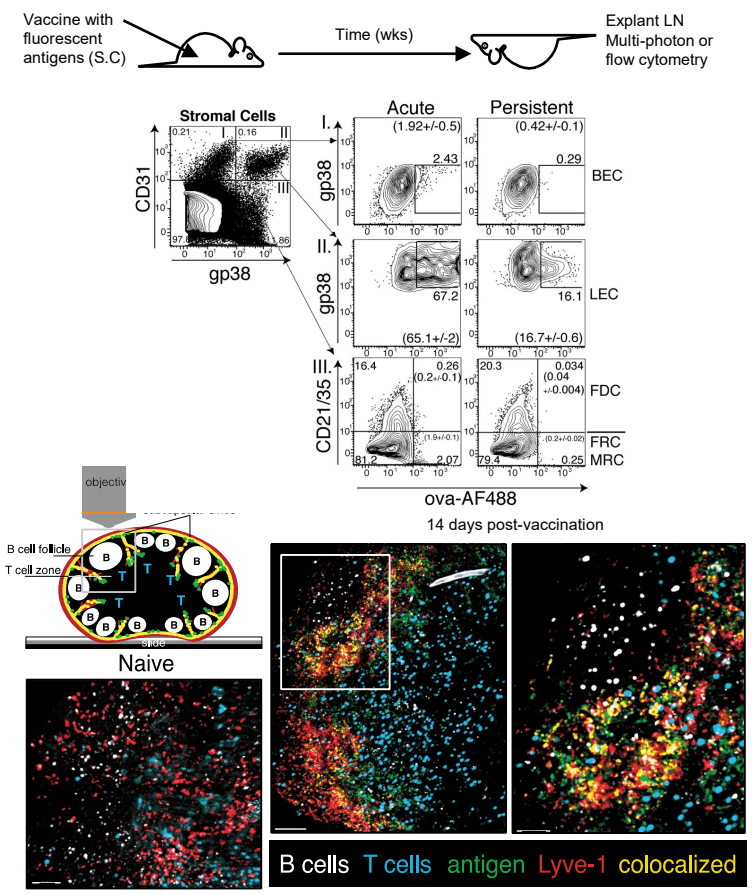


Fig. 2. Archived antigens enhanced protective immunity during re-challenge.

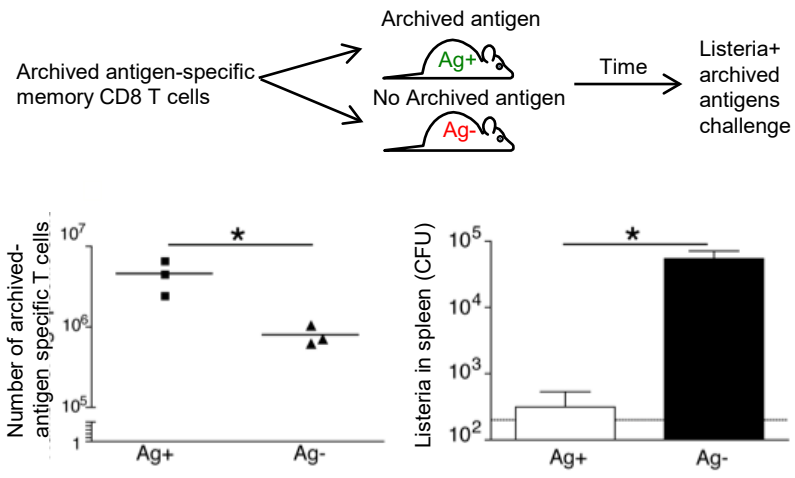


Fig. 3. LECs are undergoing apoptosis (caspase+) with a second unrelated infection at D28 and D35.

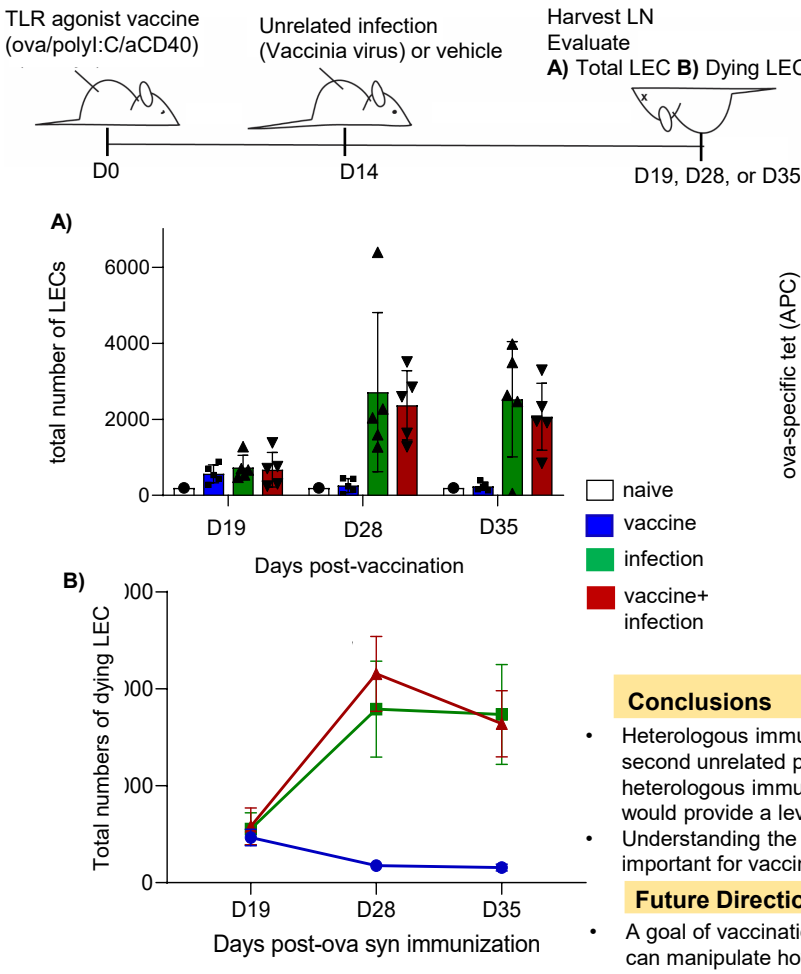


Fig. 4. As more LECs are dying, there is a boost in endogenous memory T cells following an unrelated infection.

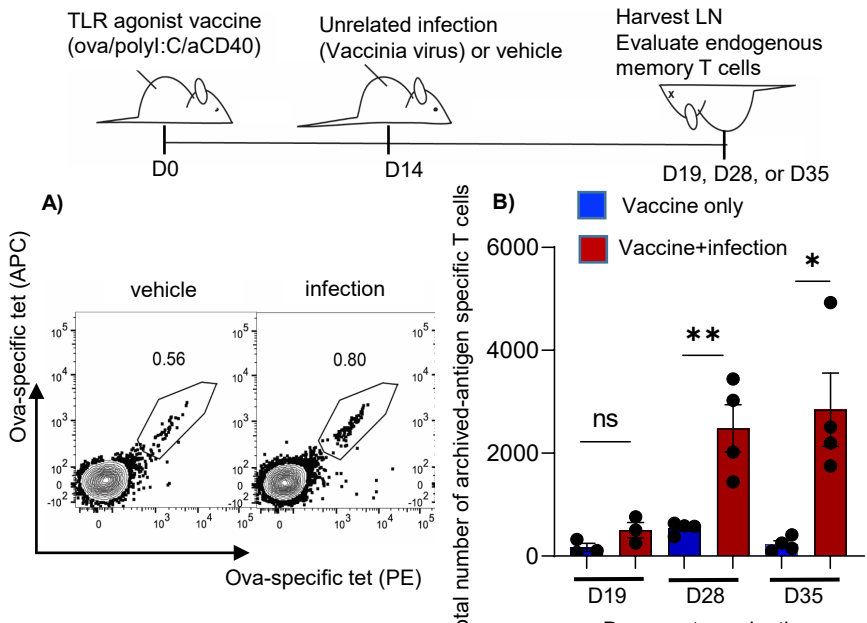
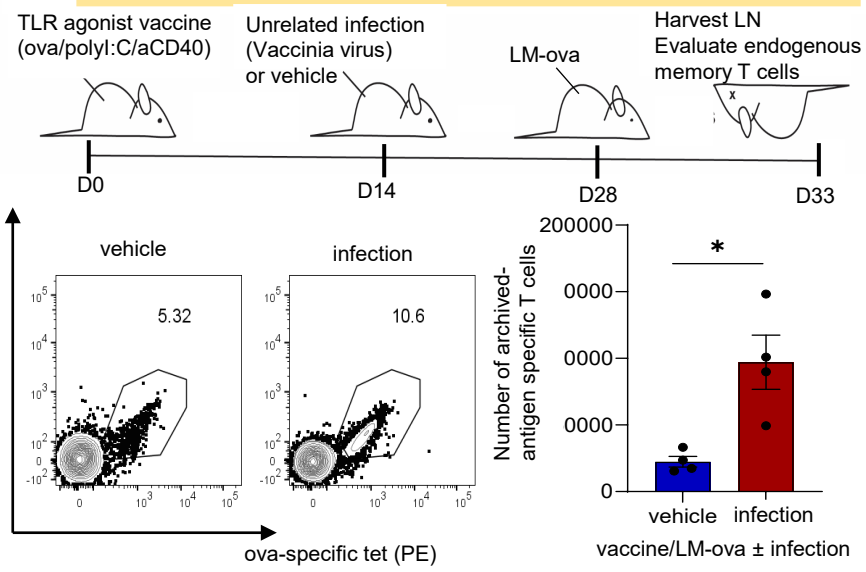


Fig. 5. Having an infection before re-challenge leads to a boost in activated archived antigens-specific T cells with an effector phenotype.



Conclusions

- Heterologous immunity is defined as a prior immune response that can provide some level of protection to a second unrelated pathogen. Thus, antigen archiving may be an underlying factor when understanding heterologous immunity as the immediate production of cytokine by archived antigen-specific memory T cells would provide a level of immunity to an unrelated pathogen.
- Understanding the process of antigen archiving and the consequences for downstream immunity will be important for vaccine design and prime-boost regimens.

Future Directions

- A goal of vaccination is to provide memory T cells to the antigen provided by the vaccine. Understanding if we can manipulate how antigens are archived or the duration of antigen archiving will benefit protective immunity.