Heterogeneous Differentiation Patterns of Individual CD8 T Cells

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Short Abstract — Upon infection, T cell populations display a highly reproducible pattern of expansion and contraction. We tracked the progeny of individual CD8 T cells by in vivo lineage tracing (molecular barcoding) and demonstrated that, even for T cells bearing identical T cell receptors, both expansion and differentiation patterns are extremely heterogeneous. Individual T cells contributed differentially to memory responses, as revealed by their participation in primary and recall infections. The discordance in fate of individual naïve T cells demonstrates that reproducibility of CD8 T cell responses is achieved through population averaging. By modeling we attempt to determine the mechanism underlying these observations.

Keywords — Molecular barcoding, heterogeneity, immune responses, stochastic modeling, individual cells.

I. INTRODUCTION

Cellular barcoding is a powerful method tracing the in vivo fate of many individual cells in a single experiment, offering opportunities to quantify the behavior of a single cell in a large population. Individual cognate T cells were tagged with collections of heritable DNA barcodes, and were transferred into mice that were subsequently infected with *Listeria monocytogenes*. At several time points during the infection, cells were isolated and assessed for their barcodes through deep sequencing [1].

II. RESULTS

The data demonstrate that huge CD8+ T cell responses are largely composed of the progeny of just a few cells, e.g., 60% of the response is accounted for by just 5% of the precursor cells. Individual CD8+ T cells that are recruited into the response expand into very different numbers of daughter cells, and this disparity in clonal expansion is established during the first phase of infection. The cellular mechanisms underlying these large differences in the progeny of identical precursors are not known. We develop different mathematical models to test different scenarios. One likely explanation is that cells differ in the time at which they enter their first division. This can be ruled out by a combination of modeling and CFSE data [1]. Alternatively, T cell families could differ in the rates by which they expand, or in the number of divisions they complete. This is currently under investigation.

Clones were also very heterogeneous in the expression of various differentiation markers, and the largest clones tended have a low expression of the early differentiation marker CD62L. We found a marked heterogeneity in the contribution of cells into a secondary response, and part of this heterogeneity can be accounted for by the expression of CD62L. Remarkably, the contribution to tertiary responses was much more predictable. Using mathematical modeling we investigate various factors determining the recruitment and subsequent expansion of individual cells from large clones into primary, secondary and tertiary responses.

III. CONCLUSION

The expansion of individual T cells into immune response is remarkably variable and heterogeneous. The observed reproducibility and robustness of primary immune responses to pathogens therefore seems a consequence of population averaging [1,2].

REFERENCES
