Time, not affinity, drives the differentiation of plasmacells from the germinal center

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Abstract

During an adaptive immune responses B cells make a series of fate decisions between becoming antibody secreting plasma cell, cycling in the germinal center and becoming a memory B cell. B cell affinity has long been assumed to be a key driver of this fate choice. However other models suggest that a temporal switch occurs and that plasma cell differentiation occurs late in the germinal center reaction. To address the role of affinity in the GC reaction we used single cell RNA-seq paired with VDJ sequencing to track single Igh^{g2A10} cells specific for the circumsporozoite protein 7 and 21 days after *Plasmodium* vaccination. Igh^{g2A10} cells have a fixed heavy chain which can pair with different light chains to form CSP specific antibodies with different affinities allowing us to link affinity to cell fate decisions. We further used CITE-seq to determine the surface expression of key markers of different populations identified transcriptomically. Using this analysis we were able to readily identify cells differentiating out of the light zone of the germinal center into either plasmacells or memory cells. We found that, in agreement with previous studies, GC cells differentiating into memory cells were generally of lower affinity than other germinal center B cells. In contrast pre-plasmacells were not of notably different affinity from other germinal center cells. However, we found that the number of cells differentiating into both plasmacells and memory cells was substantially higher at day 21 compared to day 7 providing support for a temporal switch governing the formation of high affinity long-lived plasma cells.