Homeostatic regulation of plasma cell turnover

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Abstract

Antibody-producing plasma cells (PCs) are essential for long-lasting humoral protection. A population of long-lived PCs (LLPCs) exist in both humans and in mice without the need for antigen re-exposure or memory B cell input. Whether PC longevity is imprinted at formation or cultivated over time is a fundamental question that underlies vaccination success and entails mechanisms that may be exploited in cancer scenario. Current studies have experienced technical limitations studying PCs, particularly the lack of a PC-specific genetic system.

Analysis of PC specific gene expression profiles identified *Jchain* as a candidate gene for the generation of a genetic tool, hereafter termed *Jchain*^{creERT2}. In this tool GFP-tagged creERT2 is expressed under the control of endogenous *Jchain* promoter. *Jchain* expression was reported by GFP expression and cre-activity was highly specific to PCs and occurred across immunoglobulin isotypes, allowing the first-ever PC-specific genetic manipulation *in vivo*, in their niche. Using *Jchain*^{creERT2} we timestamped PCs through expression of cre-dependent fluorescent reporter to trace cells over time.

We found that the size of the PC pool remained largely constant over the 5-month analysis, and that a reduction of genetically labelled PCs was compensated, likely by newly formed PCs, revealing homeostatically regulated population turnover. Following up on these findings we performed RNA sequencing of labelled PCs at multiple time-points over a period of 9 months after timestamping and uncovered distinct transcriptional profiles with genes that consistently increased or decreased in expression as PCs age. This led us to identify candidate transcription factors responsible for the regulation of a large fraction of genes in long-lived PCs.

By understanding PC population turnover dynamics and the determinants of PC longevity, we provide key knowledge that may allow the improvement of long-term immunity following vaccination and for therapeutic avenues in diseases of PC origin.