Plasma cells

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The secret to longevity, plasma cell style

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An enduring antibody response is ultimately dependent on the generation and maintenance of long-lived plasma cells. New research describes the use of single-cell transcriptomics approaches to reveal the defining features of longevity in plasma cells.

The longevity of the humoral immune response is a critical component for our immunity and underpins most successful immunization strategies. This protection is produced by highly specialized plasma cells that have the capacity to survive and secrete antibodies throughout the life of the host. Despite the clear importance of maintaining high antibody titers, we still have a limited understanding of the processes controlling plasma cell longevity. In this issue of *Nature Immunology*, Liu et al. report new approaches to identify long-lived plasma cells (LLPCs), revealing the heterogeneity of this compartment[1]. These findings pave the way for a better understanding of the factors impacting on the duration of antibody-mediated immunity.

Plasma cells are the end-stage of the B cell lineage. They are typically induced in secondary lymphoid organs or mucosal sites, where most plasma cells are thought to be short lived. In a poorly understood process, a small proportion of plasma cells are able to migrate to other sites, including the bone marrow, where they can become extremely long-lived antibody-producing factories[2] (Fig. 1). Studies in humans have shown that individual plasma cells can persist for many decades, as evidenced by the continued existence of plasma cells labeled by environmental ^{14}C — a product of atmospheric nuclear testing in the 1950s and 1960s[3]. The COVID-19 pandemic has seen the appreciation of the importance of a durable antibody response discussed broadly in the community, with frequent pronouncements by the media and public officials on the impact of waning antibody titers on public health measures such as vaccination schedules. It is clear that producing and maintaining LLPCs is an important parameter for the provision of protective immunity — as a consequence of natural infection and after immunization[4,5].

A key limitation preventing a better understanding of the longevity of humoral immunity has been the inability to prospectively separate the rare LLPCs from their much more abundant shorter-lived counterparts. In humans the LLPCs are thought to reside in a $CD19^-CD38^+CD138^+$ fraction of the bone marrow that contains both immunoglobulin (Ig)G- and IgA-secreting cells[6], although the extent of heterogeneity in this population is unknown. Similarly, mouse LLPCs were presumed to reside in the population of bone-marrow cells that have high expression of CD138 and the transcription factor Blimp-1 (ref. [7]), although again the makeup of this population had not been thoroughly examined at a single-cell level prior to the study of Liu and colleagues[1]. It is also known that the metabolism required for longevity is distinct from that sufficient for short-term survival, and this distinction has been used to separate these populations in both mouse and humans. LLPCs typically display higher levels of glucose uptake and expression of the amino transporter CD98, and use pyruvate for mitochondrial respiration, although these studies failed to find changes in gene expression that correlate with longevity[8].

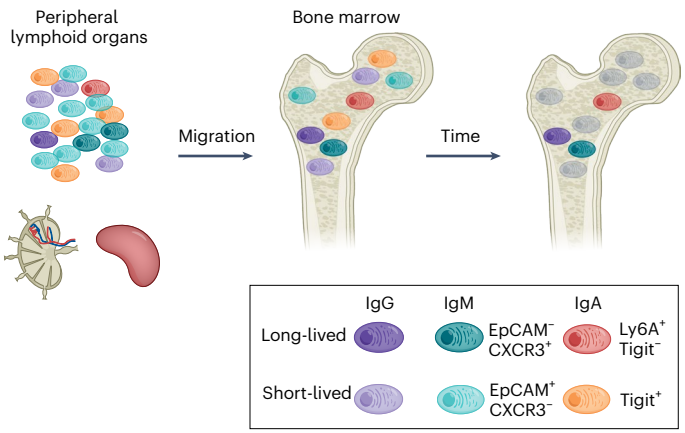

Fig. 1 | Identification of LLPCs. Plasma cells are induced in peripheral lymphoid organs and migrate to the bone marrow, where are only a small proportion become long lived. The cell surface phenotype of long-lived and short-lived plasma cells of various isotypes in mice is indicated.

Another longstanding barrier to better understanding plasma cell longevity has been their rarity. Plasma cells have been shown to represent less than 1% of bone marrow cellularity in mouse models and patient samples, and thus further fractionating these cells into biologically distinct populations has proven challenging. The development of single-cell genomic techniques has now overcome this technical limitation, and Liu et al. have combined single-cell transcriptomic analysis with sequencing of the B cell antigen receptor (BCR) to characterize plasma cells induced by protein immunization in mice[1]. These approaches, combined with time-course analysis post immunization, have identified numerous transcriptional clusters of plasma cells that also differed in their Ig isotype usage and rates of somatic hypermutation, a characteristic of germinal center–derived plasma cells. This strategy allowed the authors to identify the cluster of immunization-induced cells that persisted long term. Crucially, these putative LLPC clusters were also present in mice infected with influenza virus, and their longevity was validated using an independent genetic pulse–chase approach.

Having gained a handle on identifying LLPCs, Liu et al. were able to characterize these cells[1]. A key practical challenge for researchers in this field has been to develop prospective flow cytometry–based approaches to isolate LLPCs[7]. Mining the transcriptomic data, Liu et al. found the IgG^+ or IgM^+ LLPCs were identified as $EpCAM^+CXCR3^-$, whereas IgA^+ LLPCs were identified as $Ly6A^+Tigit^-$ (ref. [1]) (Fig. 1). That bonafide LLPCs of each isotype were identified with these cell surface phenotypes was functionally confirmed using genetic labeling

experiments. This series of observations fits with previous reports of CXCR3 being mostly associated with immature plasmablasts and EpCAM and Ly6A expression on some plasma cells[7,9,10].

The finding that plasma cells of each isotype are present in the long-lived population, and that the transcriptomes of these cells are distinct, matches recent studies in mice[11–13] and in humans[6]. It is likely that these transcriptional differences are induced by the distinct environmental milieu that promotes Ig isotype switching[13,14], although the mechanism by which these differences are maintained by LLPCs remains to be determined. It is also noteworthy that the intracellular domains of each Ig isotype are distinct and may influence the resulting transcriptome of the plasma cell.

Although previous studies have found that both T cell–independent immunization and B1 B cells could produce bone-marrow plasma cells[9], the longevity and characteristics of these plasma cells have not been determined. Liu et al. found a single cluster of IgM^+ plasma cells that lacked evidence of somatic hypermutation or N-nucleotide insertion, were T cell independent and recognized gut bacteria[1]. This cluster also contained some 'public' BCR clones that were shared across multiple mice and likely represent fetal- or neonatal-derived B1 B cells. It is probable that these clones play a homeostatic role in maintaining the symbiotic relationship between the host and its microbiota. It is also noteworthy that the mouse bone marrow contained a much higher proportion of IgM^+ plasma cells than observed in human samples[6]. Whether this difference is a consequence of the limited pathogen exposure of laboratory mice or an intrinsic difference between the humoral immune strategies of the species remains to be determined.

Although Liu et al. now provide a strategy for identifying LLPCs[1], many questions remain. Of primary importance is that we still do not have a clear understanding of why some plasma cells become long lived. One potential explanation is random chance – perhaps some plasma cells simply lodge in an appropriate niche by serendipity and then access the supporting signals to activate long-term metabolic and survival programs[15]. A more directed longevity program is also feasible as plasma cells differ in induction site, the amount of T cell help provided and BCR affinity – any of these variables may also 'instruct' longevity. In either model, the LLPCs may occupy a new survival niche or, if the available niches are limiting, outcompete existing but less fit LLPCs.

It is also unclear if the plasma cells carrying the different Ig isotypes all use the same survival mechanisms, and indeed if they all locate in the same niches in the bone marrow. Although the bone marrow is the canonical site for plasma cell longevity, it is known that the LLPCs also reside in the red pulp of the spleen and in the gastrointestinal tract[3,14]. Whether these anatomically distinct plasma cell populations use the same longevity mechanisms also remains to be determined, but is an important issue to come to grips with for the development of optimal mucosal vaccines and potentially for the treatment of antibody-mediated autoimmune diseases.

The goal for most immunization programs is sustained humoral immunity through the induction of LLPCs that provide long-term titers of high-affinity antibodies. Antigen-specific antibodies are simple to measure and provide a readout for plasma cell formation and longevity. The study of Liu et al. now offers an additional phenotypic basis for tracking LLPCs[1], at least in mice, and a framework for future research that aims to understand the molecular and cellular basis for longevity that can hopefully reveal a strategy to control the production of LLPCs as a basis for rational vaccine design.

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Competing interests

The authors declare no competing interests.