Medical & healthcare, Drug development

Identification and developmental regulation of long-lived plasma cells

Regulation of Host Defense Team, Center for Infectious Disease Education and Research

Professor Wataru Ise

Researchmap https://researchmap.jp/wataruise?lang=en

Abstract

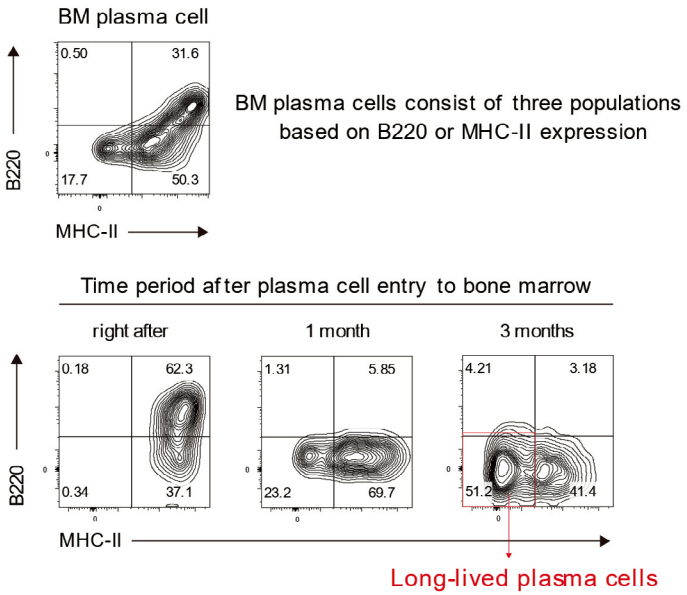
Long-term survival of plasma cells is essential for durable humoral responses and protection from viral infection. However, little is known about how newly-generated plasma cells in lymphoid tissues can achieve longevity for months or years. Here, we generated experimental system, in which plasma cells can be inducibly and irreversibly labeled so can be "time-stampled". We analyzed plasma cells survival for a year and found molecular markers that allow us to distinguish short-lived and long-lived plasma cells (LLPCs). Furthermore, We found how LLPCs are generated or where LLPCs are abundant in tissues. Finally, we demonstrated that LLPCs are sessile in survival niches. Our results will help to develop new vaccines that target efficient induction of LLPCs.

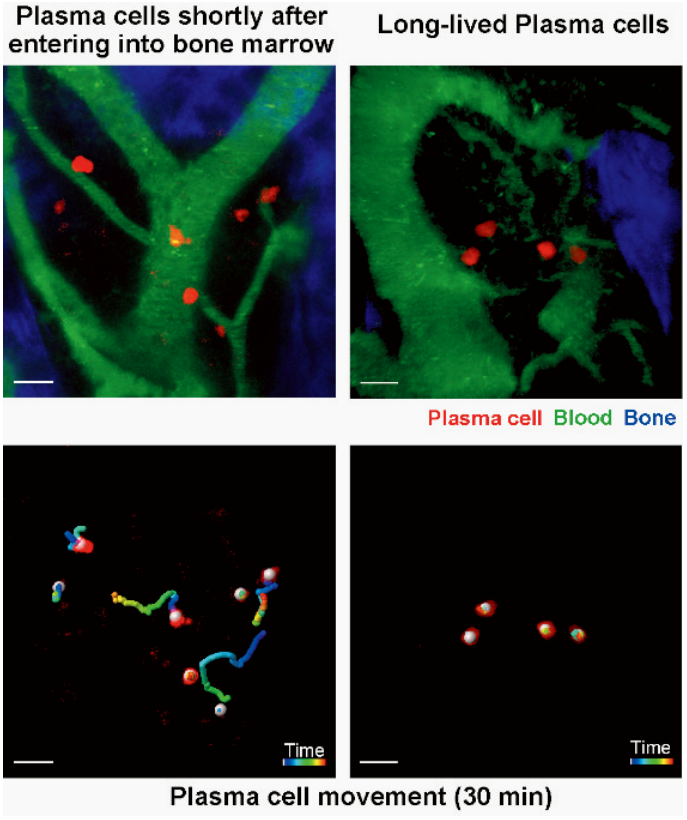
Background & Results

Neutralizing antibodies induced by vaccination are essential from viral infection. Antibodies are produced by terminally differentiated B cells, called plasma cells. A small fraction of plasma cells generated upon infection or vaccination survive for months or years in the survival niches in bone marrow (BM) or mucosal tissues, continue to produce neutralizing antibodies, and contribute to long-term protection. We've developed a new experimental system, in which the fate of plasma cells can be "time-stamped", and analyzed plasma cell survival over one year. Newly generated plasma cells were uniformly B220^{hi} MHC-II^{hi} with short-half lived but were progressively differentiated into B220^{lo} MHC-II^{lo} long-lived plasma cells (LLPCs). Such LLPCs were found in BM, spleen, or lamina propria in small intestine, but plasma cells survived longer in BM than other tissues. We also found that in the BM, germinal center (GC)-independent and GC-dependent plasma cells decayed similarly upon antigen engagement, and both entered the B220^{lo} MHC-II^{lo} LLPC pool. Intravital imaging analysis revealed that compared with B220^{hi} MHC-II^{hi} plasma cells, LLPCs were more immobilized in the BM niches and showed better survival potential. Thus, our results suggest that the adhesion status of BM plasma cells is dynamically altered during their differentiation and is associated with provision of survival signals.

Significance of the research and Future perspective

Our new experimental system allowed us to identify molecular markers of LLPCs that can distinguish from short lived plasma cells. We will isolate LLPCs from distinct tissues and analyze gene expression in more detail to clarify molecular mechanisms underlying long-term survival of plasma cells during infection or vaccination. Such studies will lead to development of new vaccine that can improve durability of antibody response.





Patent

Treatise Koike, Takuya et al. Progressive differentiation towards the long-lived plasma cell compartment in the bone marrow. Journal of Experimental Medicine. 2023, 220 (2):e20221717. doi: 10.1084/jem.20221717

URL

Keyword antibody, vaccine, plasma cell, infectious disease