Vaccine, Drug discovery

Mechanisms and biological significance of plasma cell migration to the bone marrow

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Abstract

Neutralizing antibodies, essential for protection against viral infections, are produced by plasma cells (PCs). Although most PCs generated in lymphoid tissues are intrinsically short-lived and die within a few days, a subset migrates to the bone marrow (BM), where they acquire long-term survival capacity. However, the identity of PCs capable of BM homing and the molecular mechanisms underlying this process remained unclear. In this study, we demonstrate that integrin β7-positive PCs represent the population competed to exit lymphoid tissues and enter the BM. We further identify the transcription factor KLF2 as indispensable for inducing this migratory phenotype. KLF2 promotes PC egress by upregulating S1pr1, enabling transition from lymphoid tissues into the blood. Finally, we show that KLF2-dependent PC homing to the BM is required for sustained antibody production and effective protection against viral infection.

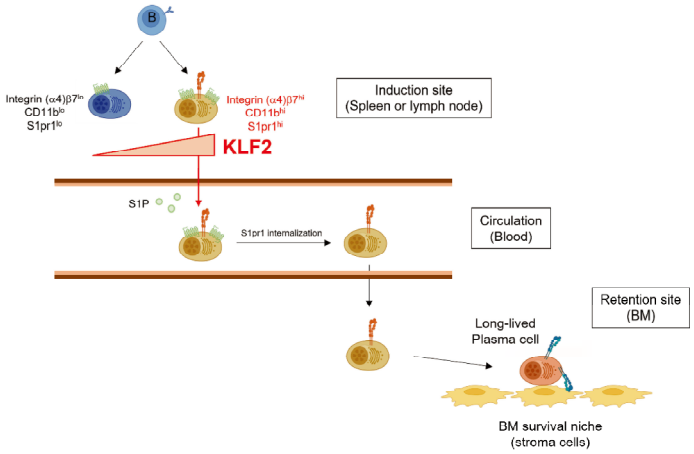
Background & Results

Vaccine-induced neutralizing antibodies are central to antiviral immunity. Because antibodies have half-lives of only days to weeks, the durability of vaccine efficacy critically depends on the lifespan of antibody-secreting PCs. While PCs generated in lymphoid organs are predominantly short-lived, a portion of them migrates to the BM and persists in specialized survival niches. Whether all PCs possess equal migratory potential or whether a dedicated subset preferentially homes to the BM had not been resolved.

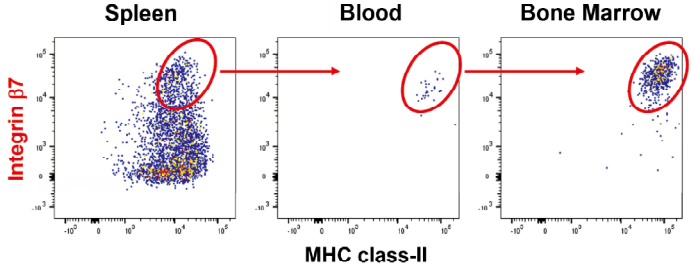
Using a protein-immunization mouse model, we found that PCs expressing integrin β7 preferentially exit lymphoid tissues, enter the circulation, and ultimately populate the BM. Loss-of-function analyses revealed that the transcription factor KLF2 is essential for generating this migratory subset: KLF2-deficient PCs fail to leave lymphoid tissues and cannot reach the BM. Mechanistically, KLF2 induces expression of the G-protein-coupled receptor S1pr1, which mediates PC egress into the blood stream. Importantly, mice lacking KLF2 specifically in germinal-center B cells exhibit impaired maintenance of vaccine-induced antibody responses and fail to mount protective immunity against influenza virus challenge.

Significance of the research and Future perspective

This study provides the first mechanistic explanation for how antibody-secreting PCs acquire the ability to migrate to BM survival niches. It also clarifies the physiological importance of this migration, demonstrating that KLF2-dependent homing of PCs is indispensable for long-lasting humoral immunity and antiviral protection. These findings highlight PC migration as a critical checkpoint in durable antibody responses and suggest that enhancing the generation of function of BM homing PCs could inform next-generation vaccine strategies aimed at improving long-term immunity.



Integrin β7^{hi} plasma cells migrate to Bone Marrow



Patent

Treatise Ise, Wataru; Koike, Takuya et al. KLF2 expression in IgG plasma cells at their induction site regulates the migration program. Journal of Experimental Medicine. 2025, 222(5), e20241019. doi: 10.1084/jem.20241019

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