CellPress

Immunity

Preview

A fast way to lose antibodies

Sheenam Verma[1] and Oliver J. Harrison[1,2,*]
[1]Benaroya Research Institute, 1201 9th Ave, Seattle, WA 98101, USA
[2]University of Washington, Department of Immunology, 750 Republican St, Seattle, WA 98109, USA
*Correspondence: oharrison@benaroyaresearch.org
https://doi.org/10.1016/j.immuni.2026.03.018

Long-lived plasma cells maintain antibody titers that sustain humoral immunity, yet the physiological cues regulating their persistence remain incompletely understood. In this issue of *Immunity*, Zhu et al. reveal that fasting-induced β-hydroxybutyrate destabilizes bone marrow plasma cell niches through HCAR2 signaling, accelerating the loss of long-lived plasma cells and humoral immunity.

Immunological memory is often viewed as a durable achievement of the adaptive immune system. Following infection or vaccination, long-lived plasma cells (LLPCs) persist in the bone marrow and continuously secrete antibodies, maintaining protective titers for years or even decades.[1,2] This capacity underlies the remarkable success of vaccines and represents one of the immune system's most effective defenses. However, despite their longevity, plasma cells occupy a precarious niche. As terminally differentiated cells devoted almost entirely to antibody secretion, they rely heavily on specialized bone marrow environments that provide survival signals and structural support.[3,4] The physiological conditions that might threaten the persistence of these long-lived effectors of humoral immunity have remained largely unclear.

In this issue of *Immunity*, Zhu and colleagues uncover an unexpected vulnerability of humoral immune memory: metabolic signals generated during fasting.[5] Their study revealed that fasting can erode established antibody responses by triggering the depletion of bone marrow plasma cells. The work identifies the ketone body β-hydroxybutyrate (BHB) as the metabolic mediator of this process and shows that BHB acts directly on plasma cells through the hydroxycarboxylic acid receptor 2 (HCAR2), destabilizing their residence within the bone marrow niche (Figure 1). These findings reveal an unexpected connection between systemic metabolic state and the durability of antibody-mediated immunity.

The authors first asked whether fasting alters the maintenance of plasma cells in bone marrow. Across several dietary patterns, including alternate-day fasting, time-restricted feeding, and prolonged fasting, they observed a significant reduction in bone marrow plasma cell numbers. Importantly, the effect extended beyond polyclonal populations. In vaccinated mice, fasting similarly reduces antigen-specific LLPCs in the bone marrow. Correspondingly, serum antibody titers declined more rapidly in fasted animals, and vaccine-induced protection against viral challenge was diminished. These findings suggest that fasting accelerates the decay of humoral immune memory by destabilizing the plasma cell compartment responsible for sustained antibody production.

What mediates this effect of nutrient deprivation on immune memory? Fasting triggers a well-known metabolic shift in which glycogen stores are depleted and fatty acid oxidation increases, leading to the production of ketone bodies in the liver.[6] Among these metabolites, BHB has emerged as a signaling molecule capable of modulating diverse physiological processes, including inflammation and cellular metabolism.[7] Zhu et al. therefore investigated whether ketone bodies generated during fasting might influence plasma cell persistence.

Metabolomic profiling revealed a pronounced increase in circulating BHB in fasted mice, consistent with the transition to ketogenesis. A ketogenic diet, which elevates ketone body production even without caloric restriction, recapitulated the loss of bone marrow plasma cells observed during fasting. Conversely, genetic disruption of ketone body synthesis prevented fasting-induced plasma cell depletion. Direct administration of BHB was sufficient to reproduce the phenotype, demonstrating that this metabolite is both necessary and sufficient to drive plasma cell loss. These experiments identified BHB as the metabolic link connecting fasting to impaired humoral immune memory.

The authors next defined the signaling pathway through which BHB acts on plasma cells. In addition to serving as an energy substrate, BHB functions as a ligand for the G-protein-coupled receptor hydroxycarboxylic acid receptor 2 (HCAR2).[8] Activation of HCAR2 triggers a signaling cascade that suppresses adenylate cyclase activity and reduces intracellular cAMP concentration.[8] Zhu et al. showed that pharmacologic activation of HCAR2 with niacin phenocopied the effects of fasting and BHB administration, leading to reduced plasma cell numbers and antigen-specific antibody titers. Conversely, deletion of HCAR2 abolished plasma cell depletion induced by fasting or BHB treatment. Genetic and bone marrow chimera experiments further demonstrated that this pathway operated directly within plasma cells themselves.

How does activation of HCAR2 ultimately lead to plasma cell loss from the bone marrow? One possibility is that fasting directly induces apoptosis of these cells. Notably, Zhu et al. found little evidence for increased plasma cell death within the bone marrow. Instead, transcriptional profiling revealed enrichment of pathways related to cell adhesion and migration. Among the most prominently affected molecules was CXCR4, a chemokine receptor that plays a central role in guiding plasma cells to bone marrow niches and retaining them there through interactions with CXCL12-producing stromal cells.[4,9]

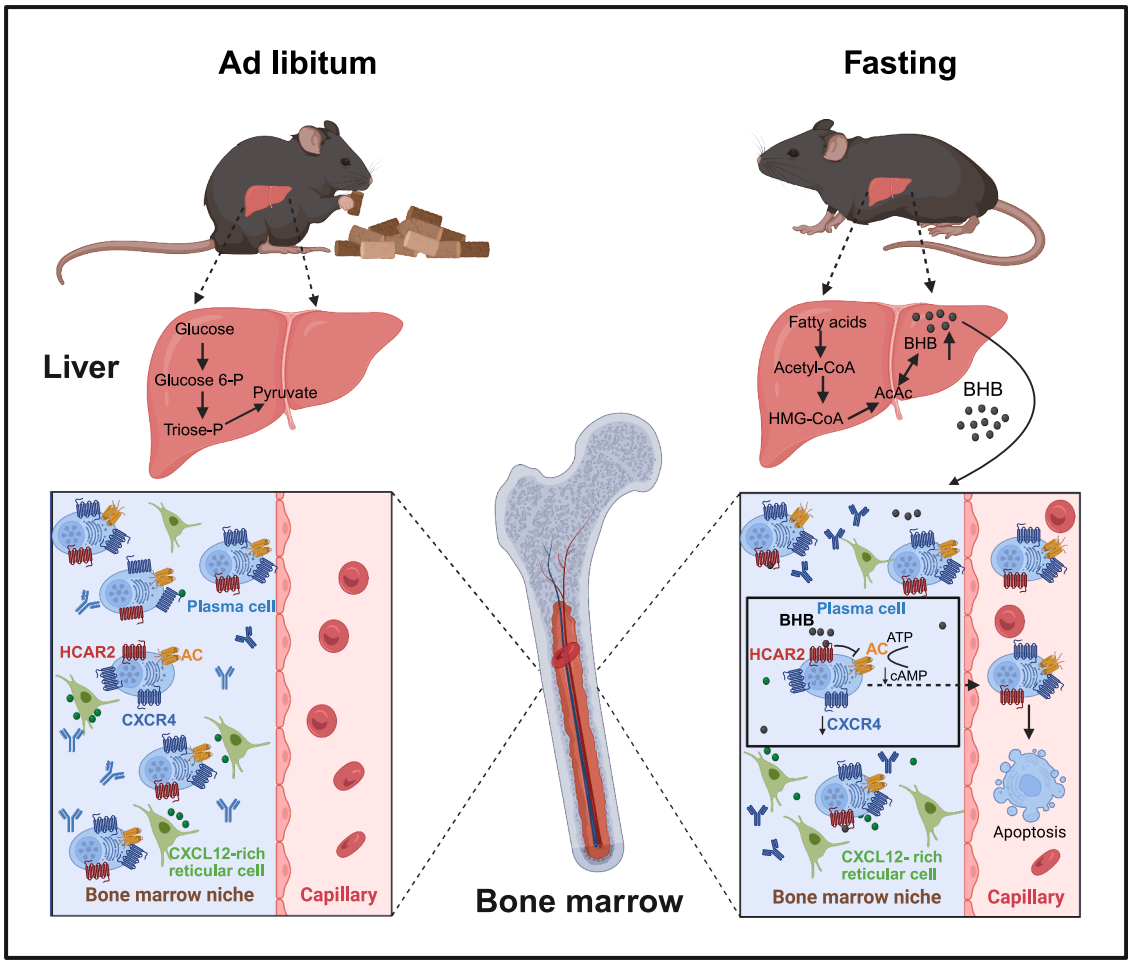

Figure 1. Fasting-induced β-hydroxybutyrate signaling drives depletion of long-lived plasma cells in the bone marrow

Under fed conditions, glucose metabolism predominates and long-lived plasma cells (LLPCs) are maintained within specialized bone marrow niches supported by CXCL12-producing stromal cells. CXCR4 expression on LLPCs drives their retention and survival within these niches. During fasting, fatty acid oxidation drives ketogenesis, elevating circulating concentrations of β-hydroxybutyrate (BHB). BHB signals through hydroxycarboxylic acid receptor 2 (HCAR2) expressed on plasma cells, inhibiting adenylate cyclase (AC) and reducing intracellular cAMP. This suppresses CXCR4 expression, disrupting niche retention and mobilizing LLPCs into the circulation, ultimately depleting the bone marrow of antigen-specific plasma cells and eroding systemic antibody titers.
Created in BioRender. Harrison, O. (2026) https://BioRender.com/k20kvgw.

Consistent with this observation, plasma cells from fasted or BHB-treated mice exhibited reduced CXCR4 expression and impaired migration toward CXCL12. Because CXCR4 is essential for anchoring plasma cells within protective bone marrow niches, its downregulation promotes their mobilization into circulation. Once displaced from these supportive microenvironments, plasma cells are deprived of the survival signals required for long-term persistence and are ultimately lost. In this way, fasting does not directly kill plasma cells but instead dislodges them from the niches that sustain their survival. Whether CXCR4 downregulation alone is sufficient to account for plasma cell loss, or whether additional niche-dependent survival signals are concurrently disrupted, remains an important question for future investigation.

These findings underscore the importance of niche residency in maintaining long-lived plasma cells. Bone marrow niches provide a constellation of survival cues, including cytokines and stromal interactions, that collectively sustain plasma cell persistence.[9,10] By linking metabolic signals to the stability of these niches, Zhu et al. have revealed an unexpected mechanism through which systemic physiology can shape the longevity of humoral immunity.

The authors extended these observations beyond mouse models by examining the impact of fasting on human volunteers. Individuals undergoing structured fasting regimens displayed elevated circulating BHB together with modest declines in antibody titers against several previously encountered viral antigens. Short-term fasting was also associated with increased numbers of circulating plasma cells, consistent with mobilization from bone marrow niches. Although the magnitude and long-term implications of these effects remain to be determined, several questions warrant further consideration. The human studies are necessarily correlative, and it remains unclear to what extent transient metabolic fluctuations during fasting are sufficient to meaningfully impact long-lived plasma cell persistence over time.

More broadly, this work adds an important dimension to the growing field of immunometabolism. Metabolic signals are increasingly recognized as key regulators of immune cell activation and differentiation, yet most studies have focused on early immune responses. Zhu et al. extend this paradigm by demonstrating that metabolic cues can also regulate the long-term maintenance of immunological memory itself. In doing so, they reveal that humoral immunity, often considered one of the most stable arms of the immune system, can be vulnerable to systemic metabolic fluctuations.

These findings also raise intriguing translational possibilities. Nutritional interventions such as fasting and ketogenic diets have attracted attention for their potential health benefits, including weight loss and improved metabolic control. The present study suggests that such interventions may also carry unintended immunological consequences. If elevated ketone bodies destabilize plasma cell niches, prolonged or repeated fasting could potentially accelerate the decay of vaccine-induced antibody responses. Although further work will be required to determine the clinical relevance of these findings, the study underscores the importance of considering metabolic context when evaluating the durability of protective immunity.

At the same time, the pathway identified by Zhu et al. may offer therapeutic opportunities. In autoimmune diseases driven by pathogenic antibodies, long-lived plasma cells are notoriously resistant to depletion. The discovery that metabolic signals can mobilize plasma cells from their survival niches suggests a potential strategy for destabilizing these otherwise persistent populations. Manipulating the BHB-HCAR2-CXCR4 axis might therefore offer a new approach for targeting autoreactive plasma cells in autoantibody-mediated disease.

Taken together, the findings of Zhu and colleagues reveal a previously unrecognized regulatory axis linking systemic metabolism to humoral immune memory. By showing that fasting-induced ketone bodies can destabilize plasma cell niches and accelerate antibody decay, this work challenges the notion that established humoral immunity is metabolically insulated. As interest in dietary interventions continues to grow, the study serves as a reminder that when it comes to immune memory, fasting may indeed be a fast way to lose antibodies.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Amanna, I.J., Carlson, N.E., and Slifka, M.K. (2007). Duration of humoral immunity to common viral and vaccine antigens. N. Engl. J. Med. *357*, 1903–1915. https://doi.org/10.1056/NEJMoa066092.

2. Halliley, J.L., Tipton, C.M., Liesveld, J., Rosenberg, A.F., Darce, J., Gregoretti, I.V., Popova, L., Kaminiski, D., Fucile, C.F., Albizua, I., et al. (2015). Long-Lived Plasma Cells Are Contained within the CD19(-)CD38(hi)CD138(+) Subset in Human Bone Marrow. Immunity *43*, 132–145. https://doi.org/10.1016/j.immuni.2015.06.016.

3. Lam, W.Y., and Bhattacharya, D. (2018). Metabolic Links between Plasma Cell Survival, Secretion, and Stress. Trends Immunol. *39*, 19–27. https://doi.org/10.1016/j.it.2017.08.007.

4. Tokoyoda, K., Egawa, T., Sugiyama, T., Choi, B.I., and Nagasawa, T. (2004). Cellular niches controlling B lymphocyte behavior within bone marrow during development. Immunity *20*, 707–718. https://doi.org/10.1016/j.immuni.2004.05.001.

5. Zhu, Y., Ding, B., Lv, H., Xu, H., Chen, J., Xu, J., Wu, Q., Hao, X., Hu, Y., Guo, J., et al. (2026). Fasting impairs humoral immunological memory by beta-hydroxybutyrate-mediated depletion of plasma cells. Immunity *59*, 1006–1024.e7. https://doi.org/10.1016/j.immuni.2026.01.002.

6. Longo, V.D., and Mattson, M.P. (2014). Fasting: molecular mechanisms and clinical applications. Cell Metab. *19*, 181–192. https://doi.org/10.1016/j.cmet.2013.12.008.

7. Youm, Y.H., Nguyen, K.Y., Grant, R.W., Goldberg, E.L., Bodogai, M., Kim, D., D'Agostino, D., Planavsky, N., Lupfer, C., Kanneganti, T.D., et al. (2015). The ketone metabolite beta-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. Nat. Med. *21*, 263–269. https://doi.org/10.1038/nm.3804.

8. Taggart, A.K.P., Kero, J., Gan, X., Cai, T.Q., Cheng, K., Ippolito, M., Ren, N., Kaplan, R., Wu, K., Wu, T.J., et al. (2005). D)-beta-Hydroxybutyrate inhibits adipocyte lipolysis via the nicotinic acid receptor PUMA-G. J. Biol. Chem. *280*, 26649–26652. https://doi.org/10.1074/jbc.C500213200.

9. Nguyen, D.C., Duan, M., Ali, M., Ley, A., Sanz, I., and Lee, F.E.H. (2021). Plasma cell survival: The intrinsic drivers, migratory signals, and extrinsic regulators. Immunol. Rev. *303*, 138–153. https://doi.org/10.1111/imr.13013.

10. Chu, V.T., Fröhlich, A., Steinhauser, G., Scheel, T., Roch, T., Fillatreau, S., Lee, J.J., Löhning, M., and Berek, C. (2011). Eosinophils are required for the maintenance of plasma cells in the bone marrow. Nat. Immunol. *12*, 151–159. https://doi.org/10.1038/ni.1981.