are being sensed by cellular Mda5 and IFIT proteins, resulting in interferon induction and translational inhibition. The West Nile virus mutant, in contrast to the coronavirus mutant, did not increase type I interferon induction. This might be explained by the presence of inhibitors of type I interferon production encoded by West Nile virus, as recently demonstrated for the closely related dengue virus[10].

The picture that emerges from these two studies is the following (**Fig. 1**). As higher eukaryotes acquired the ability to 2′-*O*-methylate their mRNAs, this opened the possibility of distinguishing self from non-self mRNA through new types of antiviral sensors, such as Mda5 and IFITs. This evolutionary advantage was counteracted by the viral acquisition of 2′-*O*-methyltransferases; coronaviruses, flaviviruses and poxviruses, among others, adopted this evasion strategy. However, this is not the only strategy used by viruses to counteract detection. Some viruses known to transcribe mRNA in the nucleus, such as the human immunodeficiency virus (HIV), use the host cell mRNA capping machinery. Other viruses, such as the influenza virus, steal the cap from the cellular mRNAs to be used as primers for initiating synthesis of their viral mRNA. Finally, picornaviruses avoid the use of a cap altogether. Instead, they use internal ribosomal entry sites, which allows cap-independent protein translation. In summary, it seems that mammalian viruses cannot afford to produce mRNA containing a cap structure lacking 2′-*O*-methylation.

The studies by Züst *et al.* and Duffis *et al.* open up new questions related to viral recognition by cellular sensors. Is non–2′-*O*-methylated mRNA directly recognized by Mda5, or are there other cellular proteins upstream of Mda5 that are required for this process? What is the molecular mechanism used by the IFIT proteins to preferentially mediate translational arrest of non–2′-*O*-methylated mRNA? Do other RNA modifications and cellular sensors participate in the distinction between self and non-self RNA? Can this information be used to design new antiviral inhibitors? Future studies are needed to elucidate these intriguing and interesting questions emerging from the millions of years of coevolution between viruses and hosts.

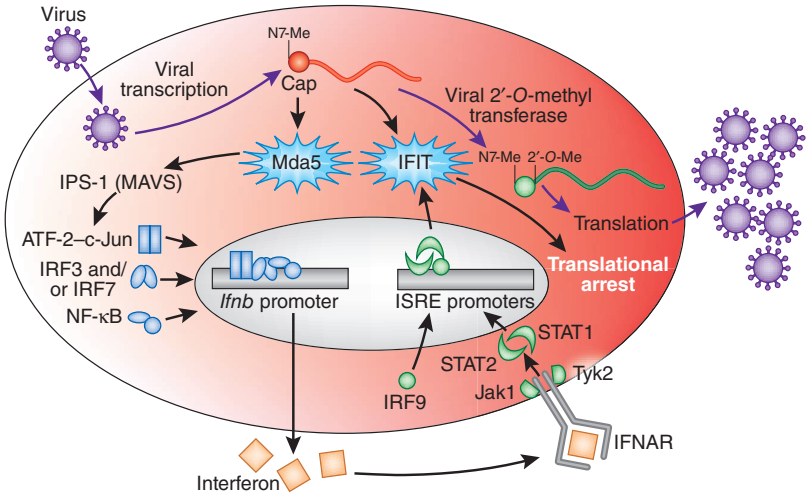

Figure 1 2′-*O*-methylation of viral mRNA avoids recognition by the cellular antiviral sensing machinery. In the case of viruses that replicate in the cytoplasm and do not have access to the cellular nuclear machinery responsible for mRNA capping, viral mRNA is synthesized by viral enzymes. Thus, many cytoplasmic viruses encode the functions required to cap and N7-methylate the viral mRNA. Although N7 methylation is sufficient to access the cellular translation machinery, 2′-*O*-methylation of the viral mRNA is also needed for it to avoid detection. In the absence of 2′-*O*-methylation, mRNAs induce the activation of the cellular sensor Mda5, which interacts with the downstream molecule IPS-1 (also called MAVS), resulting in activation of the latent transcription factors ATF-2, c-Jun, IRF3 and/or IRF7, and NF-κB, followed by type I interferon synthesis and secretion. Interferon binds to the interferon receptor IFNAR and initiates a signaling cascade involving the Jak1 and Tyk2 kinases and a transcription complex composed of STAT1, STAT2 and IRF9. This complex initiates the transcription of interferon-stimulated response element (ISRE) antiviral genes, such as the interferon-induced proteins with tricopeptide repeats (IFIT). IFITs inhibit cap-dependent translation, with a preference for mRNAs lacking 2′-*O*-methylation. Me, methyl; *Ifnb*, interferon-β gene.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

1. Züst, R. *et al. Nat. Immunol.* **12**, 137–143 (2011).
2. Daffis, S. *et al. Nature* **468**, 452–456 (2010).
3. Yoneyama, M. *et al. Nat. Immunol.* **5**, 730–737 (2004).
4. Hornung, V. *et al. Science* **314**, 994–997 (2006).
5. Cui, S. *et al. Mol. Cell* **29**, 169–179 (2008).
6. Rehwinkel, J. *et al. Cell* **140**, 397–408 (2010).
7. Baum, A., Sachidanandam, R. & García-Sastre, A. *Proc. Natl. Acad. Sci. USA* **107**, 16303–16308 (2010).
8. Kato, H. *et al. J. Exp. Med.* **205**, 1601–1610 (2008).
9. Hui, D.J., Terenzi, F., Merrick, W.C. & Sen, G.C. *J. Biol. Chem.* **280**, 3433–3440 (2005).
10. Rodriguez-Madoz, J.R. *et al. J. Virol.* **84**, 9760–9774 (2010).

New friends for bone marrow plasma cells

Robert Brink

Long-lived plasma cells require a specialized bone marrow microenvironment in order to survive and produce antibody. Eosinophils make an important contribution to maintaining this survival niche.

The bone marrow is one of the great cellular factories of the body, replenishing the stocks of nearly every cell type that makes up the immune system. Among these are the B lymphocytes, whose task is to produce the secreted antibody proteins that bind to and eliminate invading foreign antigens. The development of B cells within the bone marrow occurs within specialized microenvironments, or niches, that provide the nourishment required to keep precursor cells alive and committed to their job of producing the next generation of B cells[1] (**Fig. 1**). After moving out of the bone marrow and into the periphery, mature B cells may be activated by foreign antigen, migrate into germinal centers and eventually emerge as plasmablasts encoding antibodies that can now bind foreign antigen with increased affinity (**Fig. 1**). These cells ultimately return to the bone marrow

Robert Brink is in the Immunology Program, Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia.
e-mail: r.brink@garvan.org.au

as terminally differentiated plasma cells, where they launch high-affinity antibodies into the circulation to seek out and destroy the invading foreign antigen (**Fig. 1**). Plasma cells also require support and nourishment in a specialized bone marrow niche. Although the plasma cell niche is known to be distinct from the niche that sustains early B cell precursors[1] (**Fig. 1**), it remains otherwise poorly defined. In this issue of *Nature Immunology*[2], Chu, Berek and colleagues present new evidence that eosinophils make a key contribution to supporting the long-term survival of bone marrow plasma cells. This somewhat surprising finding indicates that multiple cell types collaborate to maintain the bone marrow plasma cell survival niche.

Much of the previous work identifying plasma cell survival factors has been performed using *in vitro* systems involving the addition of recombinant cytokines or *ex vivo* cell preparations. Although this work has been important in indicating what could be happening *in vivo*, the specialized nature of survival niches makes a particularly strong case for *in vivo* experimentation to identify which cells and molecules actually do the job. The relative inaccessibility of the bone marrow, as opposed to peripheral lymphoid organs such as the spleen and lymph nodes, has been a major obstacle in this respect. However, it was recently shown that over 90% of plasma cells in the bone marrow are associated with CXCL12-expressing mesenchymal stromal cells[1]. Plasma cells express high amounts of CXCR4, the receptor for CXCL12, and this receptor seems to have an important role not only in the homing of plasma cells to the bone marrow but also in their survival there. *In vivo* experiments have also revealed key roles for the TNF family cytokine APRIL and its receptor BCMA in maintaining plasma cell survival in the bone marrow[3,4]. However, APRIL is poorly expressed by the CXCL12$^+$ bone marrow stromal cells[3], indicating that separate APRIL-expressing cell(s) are likely to be involved in this process. Identification of this unknown bone marrow cell was the starting point for the study of Chu *et al.*[2].

The authors surveyed different populations of cells extracted from the bone marrow for APRIL secretion. The highest producers turned out to be the resident eosinophils, identifiable as such by the strong staining of their cytoplasmic vesicles with the acidic dye eosin and by their characteristic lobular nuclei[5] (**Fig. 1**). They next performed several *in vitro* experiments that strongly implied that eosinophils have an important role in supporting plasma cell survival. However, the most conclusive evidence came from a series of *in vivo* observations and experiments.

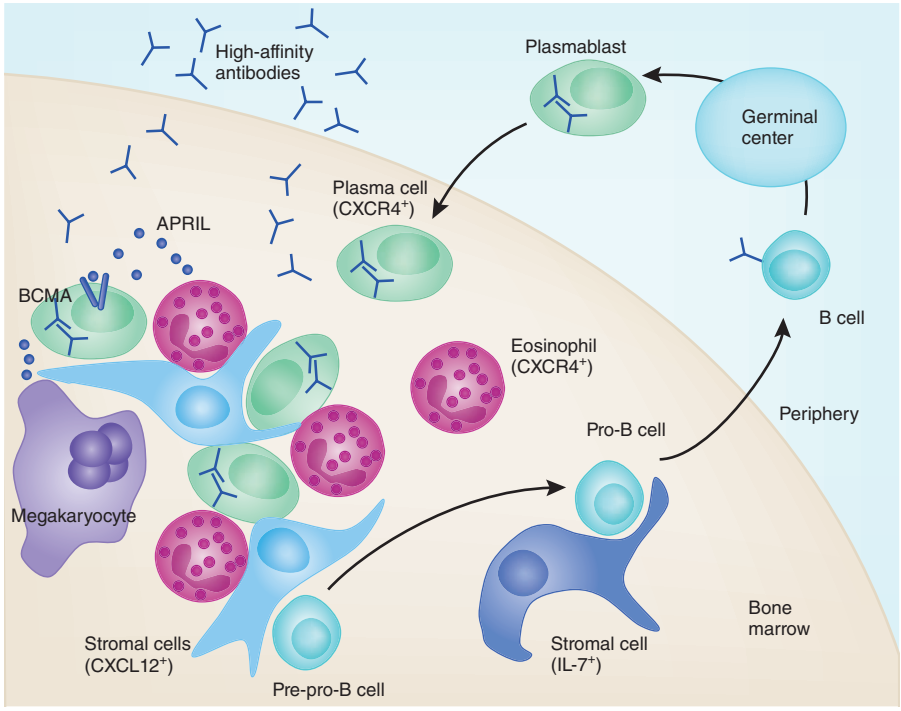

Figure 1 Bone marrow survival niches for early and late-stage B cells. Mature, peripheral B cells that are activated by foreign antigen (such as a virus) enter the germinal center reaction. They emerge as proliferating plasmablasts, which in turn differentiate into plasma cells capable of producing high-affinity antibodies against the foreign antigen. Expression of the homing receptor CXCR4 by plasma cells guides them to the bone marrow, where they localize with stromal cells expressing the CXCR4 ligand, CXCL12, and secrete antibody. Bone marrow eosinophils also express CXCR4, and join with stromal cells and plasma cells to form the plasma cell survival niche. Eosinophils participate by secreting APRIL, which delivers survival signals to plasma cells through their BCMA receptors. Megakaryocytes may also contribute to plasma cell survival by secreting APRIL. Very early B cell precursors (pre-pro-B cells) also associate with the CXCL12$^+$ stromal cells but later develop into pro-B cells that require an independent survival niche based on IL-7$^+$ stromal cells.

First, *in situ* analysis of the bone marrow showed that APRIL-expressing eosinophils localize in close proximity to both bone marrow plasma cells and the CXCL12$^+$VACM-1$^+$ stromal cells previously identified as essential for their maintenance[1] (**Fig. 1**). Like plasma cells, eosinophils express the CXCL12 receptor CXCR4 (ref. 6), making this the most likely means by which they are attracted to the plasma cell niche. Second, two mutant mouse strains genetically deficient in eosinophils (ΔdblGATA-1 and PHIL) have greatly reduced APRIL expression in the bone marrow as well as significant depletion of bone marrow plasma cells[2]. That the absence of eosinophils was directly responsible for this phenotype was indicated by the temporary, albeit partial, boost in bone marrow plasma cells that occurred after the transfer of wild-type eosinophils into these mice[2]. Lastly, antibody-mediated depletion of eosinophils led to the apoptosis and overall depletion of bone marrow plasma cells in wild-type mice[2].

Eosinophils are best known for mediating inflammatory responses against parasitic worms or allergic inflammation in the asthmatic lung. However, it has recently become apparent that eosinophils perform a diverse range of functions *in vivo* that do not necessarily involve inflammation[5]. The role of eosinophils in the plasma cell niche is therefore another example of the versatility of this cell type. Interestingly, megakaryocytes, a separate hematopoietic cell type involved in the production of blood clot-forming platelets, can also produce APRIL and may be involved in the bone marrow plasma cell niche[7] (**Fig. 1**). The participation of other cell types in the plasma cell niche is consistent with the results of Chu *et al.*, as ablation of eosinophils reduced but did not completely eliminate bone marrow plasma cells[2]. However, it seems clear that eosinophils have a key role in this niche, and establishing eosinophil-targeted therapies now seems to be a viable new option in manipulating bone marrow plasma cell numbers.

An important factor in considering therapies that target the plasma cell niche is that, like all the specialized hematopoietic niches within the bone marrow, it is of limited

size[8,9]. Thus, plasma cells are typically present at low but relatively constant frequencies (~0.5%) within the bone marrow, implying that newly generated plasma cells must compete with resident cells for the limited space and survival signals available in the plasma cell niche[10]. The limited capacity of this niche provides a potential opportunity to manipulate plasma cell survival in a variety of clinically relevant settings. For instance, optimizing the contribution of newly generated plasma cells to the bone marrow niche may significantly boost long-term antibody production after vaccination. On the flip side, it may also be possible to target the survival signals that support malignant bone marrow plasma cells in the currently intractable cancer multiple myeloma.

An area in which targeting of the pro-survival functions of eosinophils might be most immediately useful is in autoimmune diseases driven by autoantibodies derived from bone marrow plasma cells. For instance, therapies that efficiently eliminate peripheral B cells and that are often used to treat antibody-mediated autoimmune diseases do not affect bone marrow plasma cell survival or long-term antibody production[11]. The findings of Chu *et al.* establish a strong case for replacing or supplementing such approaches with therapies that eliminate or neutralize bone marrow eosinophils in order to 'starve' autoantibody-producing plasma cells residing in the bone marrow. In this way, the new-found friends of the bone marrow plasma cells may provide a fresh target in controlling the rogue element within the plasma cell niche.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

1. Tokoyoda, K., Egawa, T., Sugiyama, T., Choi, B.-I. & Nagasawa, T. *Immunity* **20**, 707–718 (2004).
2. Chu, V.T. *et al. Nat. Immunol.* **12**, 151–159 (2011).
3. Belnoue, E. *et al. Blood* **111**, 2755–2764 (2008).
4. O'Connor, B.P. *et al. J. Exp. Med.* **199**, 91–98 (2004).
5. Rothenberg, M.E. & Hogan, S.P. *Annu. Rev. Immunol.* **24**, 147–174 (2006).
6. Ma, Q., Jones, D. & Springer, T.A. *Immunity* **10**, 463–471 (1999).
7. Winter, O. *et al. Blood* **116**, 1867–1875 (2010).
8. Tokoyoda, K., Hauser, A.E., Nakayama, T. & Radbruch, A. *Nat. Rev. Immunol.* **10**, 193–200 (2010).
9. Oh, I.H. & Kwon, K.R. *Stem Cells* **28**, 1243–1249 (2010).
10. Manz, R.A., Hauser, A.E., Hiepe, F. & Radbruch, A. *Annu. Rev. Immunol.* **23**, 367–386 (2005).
11. DiLillo, D.J. *et al. J. Immunol.* **180**, 361–371 (2008).