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INSIGHTS

TACItness MZ B cell maturation

Mauricio Guzmán[1], Martyna Filipska[1], and Andrea Cerutti[1,2]

In this issue, Luff et al. (https://doi.org/10.1084/jem.20251308) show that cell-intrinsic signals from TACI drive marginal zone B cell development from T2 B cells through a mechanism involving activation of the PI3K–AKT pathway and inhibition of the FOXO1-KLF2 axis.

Splenic marginal zone (MZ) B cells differentiate from transitional 2 (T2) B cells through a mechanism involving the B cell receptor (BCR) and NOTCH2 (Cerutti et al., 2013) and mount rapid T cell–independent (TI) antibody responses to blood-borne antigens (Cerutti et al., 2013). A study by Luff et al. (2026) demonstrated that cell-intrinsic signals from transmembrane activator and CAML interactor (TACI) contribute to the development of MZ B cells in mice. TACI stimulated this process by activating PI3K and AKT kinase while inactivating FOXO1. These findings change the earlier view that TACI inhibits peripheral B cell survival (Yan et al., 2001).

MZ B cells and plasma cells (PCs) highly express the TACI receptor, which is also expressed by follicular (FO) B cells, albeit to a lesser extent (Mackay and Schneider, 2009). TACI engages both B cell–activating factor of the TNF family (BAFF) and a proliferation-inducing ligand (APRIL), two structurally related molecules (Mackay and Schneider, 2009). In addition to TACI, BAFF engages BAFF receptor (BAFF-R) on B cells and B cell maturation antigen (BCMA) on PCs, whereas APRIL engages TACI and BCMA but not BAFF-R (Mackay and Schneider, 2009). While BAFF-R mainly drives B cell survival (Schweighoffer et al., 2013), TACI elicits class switching and PC differentiation (von Bülow et al., 2001; Castigli et al., 2005; Salzer et al., 2005; Sintes et al., 2017; Grasset et al., 2020). Finally, BCMA stimulates PC survival, although this effect may be less intense than initially thought (O'Connor et al., 2004; Menzel et al., 2025).

By showing massive expansion of FO and MZ B cells, initial observations from TACI-deficient mice were interpreted as the demonstration that TACI inhibits B cell survival (Yan et al., 2001). At the same time, splenic MZ or gut B cells from TACI-deficient mice exhibit a severe impairment of TI IgM production, IgG or IgA class switching, and PC differentiation (von Bülow et al., 2001; Sintes et al., 2017; Grasset et al., 2020). These positive effects of TACI are at odds with the purported negative impact of TACI on B cell survival (Yan et al., 2001). A clue for the solution of this apparent paradox may be provided by the increase of serum BAFF in TACI-deficient mice (Sintes et al., 2017; Grasset et al., 2020), which is likely caused by the reduction of BAFF-binding capacity in TACI-deficient mice. Given that BAFF-R is the only prominent BAFF-binding molecule in these mice, BAFF-R would transduce unrestrained survival signals to B cells (see panel A in the figure).

To gain new insights into BAFF-R signaling and better understand its impact on TACI deficiency, Luff et al. (2026) generated mice expressing tagged BAFF-R-TwinStrepTag by CRISPR/Cas9 editing and then activated B cells from these mice with LPS with or without BAFF. Immunoprecipitation of tagged BAFF-R was followed by mass spectrometry. Unexpectedly, TACI co-immunoprecipitated with BAFF-R in BAFF-stimulated but not control B cells, showing that TACI interacts with BAFF-R in response to BAFF.

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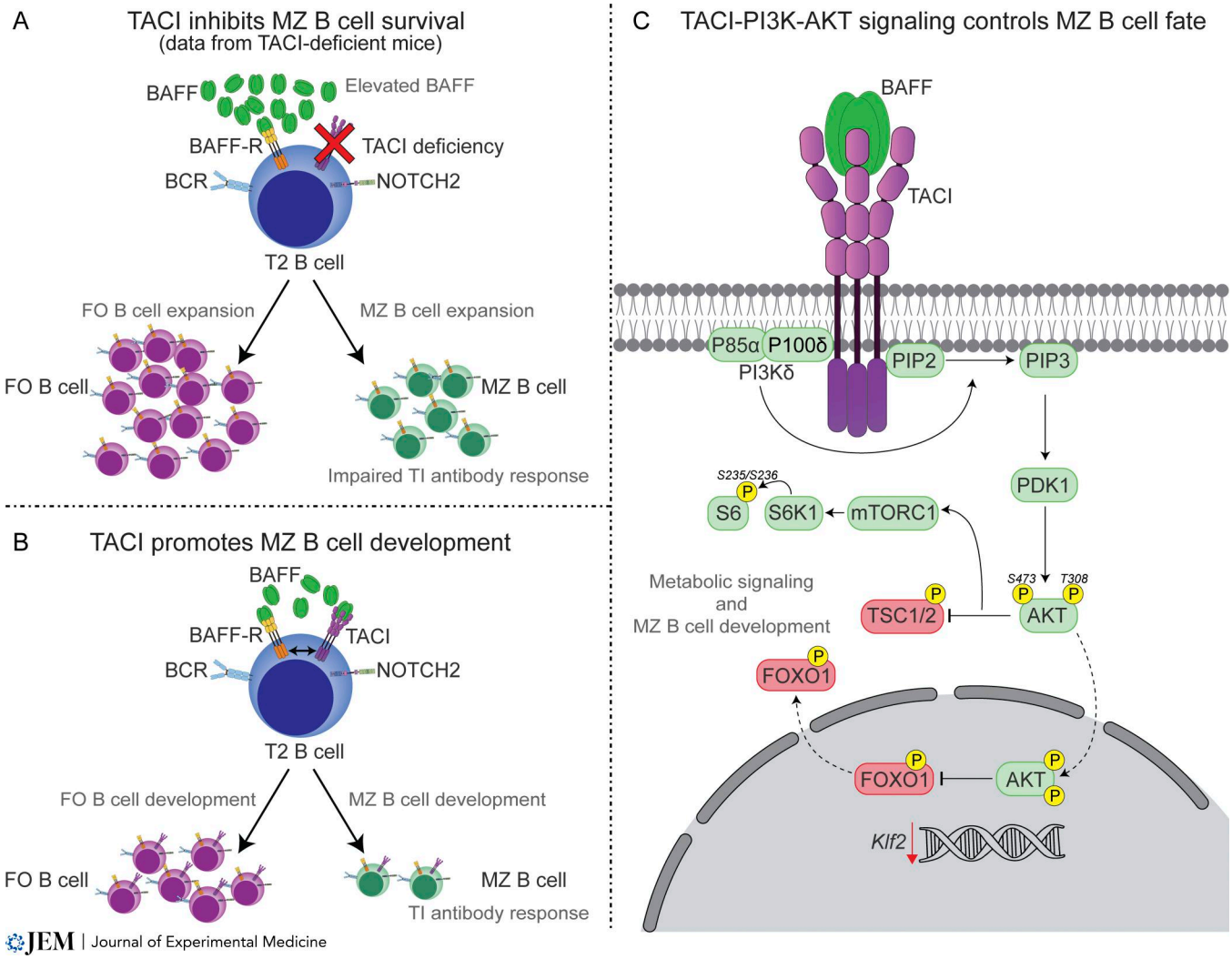
When B cells from TACI-deficient mice were analyzed, Luff et al. (2026) found that the proportion of splenic MZ B cells was reduced due to the massive expansion of splenic FO B cells, suggesting that TACI might not inhibit MZ B cell survival. However, the B cell–intrinsic activity of TACI could not be determined by simply comparing WT controls and *Tnfrsf13b*$^{-/-}$ (TACI-KO) mice, as B cells from the latter mice have abnormally increased BAFF-R signaling.

To bypass this confounding factor, Luff et al. (2026) generated clever mixed TACI-KO:WT and control WT:WT bone marrow chimeras by reconstituting irradiated *Rag1*$^{-/-}$ B6 mice with bone marrow from CD45.2-expressing *Tnfrsf13b*$^{-/-}$ or *Tnfrsf13b*$^{+/+}$ B6 mice mixed with bone marrow from CD45.1-expressing WT B6 mice. Remarkably, circulating BAFF was comparable in both sets of chimeras, and TACI-KO:WT chimeras showed no B cells hyperplasia, suggesting that TACI deficiency plays no role in the genesis of B cell expansion.

Having established that mixed TACI-KO:WT chimeras could be used to study the B cell–intrinsic effects of TACI deficiency,

[1]Barcelona Biomedical Research Park, Hospital del Mar Research Institute Barcelona (HMRIB), Barcelona, Spain; [2]Barcelona Biomedical Research Park, Catalan Institute for Research and Advanced Studies (ICREA), Barcelona, Spain.

Correspondence to Andrea Cerutti: acerutti@researchmar.net.



The understanding of TACI function over time. (A) The initial analysis of TACI-deficient mice (2001–2003) indicated that TACI inhibited B cell survival because both FO and MZ B cells were expanded. Subsequent studies determined that TACI deficiency increased BAFF, suggesting that abnormally high BAFF-R signaling caused the B cell expansion. The differentiation of MZ B cells from T2 B cells was mostly attributed to BCR and NOTCH2 receptors, with a BAFF-R component found at a later time. (B) Luff et al. (2026) show that TACI interacts with BAFF-R in response to BAFF and promotes T2 B cell differentiation into MZ B cells through a mechanism likely involving cooperation with BAFF-R as well as BCR and NOTCH2. (C) Luff et al. (2026) show that TACI stimulates T2 B cell differentiation into MZ B cells via a PI3K–AKT pathway, leading to KLF2-facilitated FOXO inactivation. By inhibiting the TSC1–TSC2 mTORC1 suppressor complex, the PI3K–AKT pathway also activates mTORC1, which further contributes to MZ B cell development in addition to enhancing MZ B cell metabolic fitness.

Luff et al. (2026) confirmed the reduction of MZ but not T2 or FO B cells in TACI-KO:WT chimeras compared with WT:WT controls. This finding suggested the involvement of TACI signaling in MZ B cell development. Such a conclusion was further supported by the analysis of TACI-KO:WT and WT-WT control chimeras, which were generated by reconstituting irradiated *Rag1*$^{-/-}$ B6 mice with bone marrow from either *Tnfrsf13b*$^{-/-}$ or *Tnfrsf13b*$^{+/+}$ B6 mice mixed with bone marrow cells from WT 129 mice. In this model, Ly9.2-expressing TACI-deficient MZ but not FO B cells were decreased in TACI-KO:WT chimeras compared with Ly9.1-expressing MZ and FO B cells from WT-WT control chimeras. Moreover, IgH^{b}-IgM and IgH^{b}-IgG1 responses were impaired in TACI-KO:WT chimeras immunized with a common TI antigen compared with IgH^{a}-IgM and IgH^{a}-IgG1 responses in similarly immunized WT-WT controls.

Given that TACI interacted with BAFF-R in BAFF-stimulated B cells, Luff et al. (2026) went on to exclude any involvement of TACI in the inhibition of MZ B cell survival. *In vivo* DNA labeling demonstrated that the loss of TACI affected neither the proliferation nor the survival of MZ B cells in the mixed chimeras. Additional experiments involving the adoptive transfer of splenic B cells from mixed chimeras into CD45.1^{+}CD45.2^{+} recipients indicated that TACI deficiency did not affect the homing of MZ B cells either. Altogether, these results indicate that TACI mediates the development of MZ B cells from immature T2 B cell precursors rather than regulating the survival and/or homing of MZ B cells (see panel B in the figure).

Accordingly, TACI-deficient MZ B cells from TACI-KO-WT chimeras expressed a "FO-like" phenotype characterized by lower CD1d, CD21, and IgM expression but increased CD23 and IgD expression compared with WT MZ B cells. These phenotypic

differences were backed up by transcriptome studies. Gene set enrichment analysis further supported the role of TACI in MZ B cell development by showing an increased FOXO1 activity in B cells lacking TACI, including increased expression of FOXO1-activated genes, such as *Klf2*.

Of note, the increased FOXO1 activity was paralleled by a decreased AKT1 activity. Considering that AKT orchestrates MZ B cell differentiation by turning off FOXO1 (Cox et al., 2023), these findings indicate that TACI promotes MZ B cell development from T2 B cells by eliciting AKT-mediated inactivation of FOXO1 (see panel C in the figure). In addition to inhibiting the FOXO1 pathway, AKT1 activates the mTOR complex 1 (mTORC1) pathway, which similarly contributes to the activation of human MZ B cells by APRIL via TACI (Sintes et al., 2017). In agreement with this last study, Luff et al. (2026) determined that TACI-deficient MZ B cells exhibited decreased activity of both AKT1 and mTORC1.

Consistent with the notion that PI3K is needed for the activation of AKT and that the PI3K pathway is involved in the TACI-mediated activation of human MZ B cells through APRIL (Sintes et al., 2017), Luff et al. (2026) also found that TACI constitutively associated with both PI3K and mTOR, suggesting that TACI can activate mTORC1 by nucleating PI3K to the plasma membrane (see panel C in the figure). The constitutive association of TACI with mTOR in MZ B cells is also shown by an earlier human work (Sintes et al., 2017) and may reflect persistent TACI signaling resulting from steady-state release of TACI ligands by myeloid, lymphoid, and stromal cells in the MZ.

At variance with the human study (Sintes et al., 2017), the mouse study from Luff et al. (2026) shows that MZ B cell exposure to BAFF or APRIL neither enhanced mTOR association to TACI nor elicited MyD88 recruitment to TACI. Such differences could stem from some well-known species specific peculiarities of TACI, including the presence of distinct ratios of long and short TACI isoforms at distinct stages of human B cell differentiation (Garcia-Carmona et al., 2023). An additional difference may relate to human B cell expression of APRIL, which signals through short TACI (Garcia-Carmona et al., 2023).

Notwithstanding these differences, the study by Luff et al. (2026) is highly complementary to the earlier human work (Sintes et al., 2017), which also highlights the involvement of PI3K, AKT, and mTORC1 in TACI-stimulated MZ B cells. More importantly, Luff et al. (2026) show for the first time that TACI stimulates the differentiation of MZ B cells from T2 cells. This seminal finding opens a number of intriguing questions. Does TACI cooperate with NOTCH2 and/or the BCR to elicit MZ B cell development from T2 precursors (Schweighoffer et al., 2013)? Does this cooperation involve the physical association of TACI with NOTCH2 and/or the BCR? Does TACI activate the serine/threonine kinase Taok3 and the metalloprotease ADAM10 (Hammad et al., 2017), which are central to BCR-induced MZ B cell development? What is the contribution of BAFF-R to TACI signaling in light of the close interaction between these receptors in BAFF-activated B cells? And finally, are BAFF trimers sufficient to activate combined TACI and BAFF-R signaling, or does this signaling need higher order BAFF oligomers? The fun has just begun.

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References

Castigli, E., et al. 2005. *J. Exp. Med.* https://doi.org/10.1084/jem.20032000
Cerutti, A., et al. 2013. *Nat. Rev. Immunol.* https://doi.org/10.1038/nri3383
Cox, E.-M., et al. 2023. *Cell Rep.* https://doi.org/10.1016/j.celrep.2023.112378
Garcia-Carmona, Y., et al. 2023. *Clin. Immunol.* https://doi.org/10.1016/j.clim.2023.109689
Grasset, E.K., et al. 2020. *Sci. Immunol.* https://doi.org/10.1126/sciimmunol.aat7117
Hammad, H., et al. 2017. *Nat. Immunol.* https://doi.org/10.1038/ni.3657
Luff, D.H., et al. 2026. *J. Exp. Med.* https://doi.org/10.1084/jem.20251308
Mackay, F., and P. Schneider. 2009. *Nat. Rev. Immunol.* https://doi.org/10.1038/nri2572
Menzel, S.R., et al. 2025. *Nat. Commun.* https://doi.org/10.1038/s41467-025-62530-2
O'Connor, B.P., et al. 2004. *J. Exp. Med.* https://doi.org/10.1084/jem.20031330
Salzer, U., et al. 2005. *Nat. Genet.* https://doi.org/10.1038/ng1600
Schweighoffer, E., et al. 2013. *Immunity*. https://doi.org/10.1016/j.immuni.2012.11.015
Sintes, J., et al. 2017. *Nat. Commun.* https://doi.org/10.1038/s41467-017-01602-4
von Bülow, G.U., et al. 2001. *Immunity*. https://doi.org/10.1016/s1074-7613(01)00130-3
Yan, M., et al. 2001. *Nat. Immunol.* https://doi.org/10.1038/89790