The periphery, the size of the recirculating B-cell pool in the secondary lymphoid organs depends on the interaction of BAFFR (B-cell-activating factor receptor, TNFRSF13C) with its ligand BAFF (BlyS) (Thompson et al., 2001). Binding of BAFF to BAFFR triggers via NIK-/IKK1-dependent signaling the processing of NF-κB2 from the p100 to the p52 form. This, besides the activation of PI3K, alters gene expression and ultimately favors cellular survival. A recent study (Schweighoffer et al., 2013) provided first surprising evidence that Syk, apart from its function in tonic BCR signaling, acts as a BAFFR signaling hub by being activated upon BAFFR stimulation and feeding into the PI3K pathway. Yet, it remained unclear how BAFFR communicates with the BCR signaling subunits (Fig 1A).

By applying an elegant, inducible, and B-cell-specific Syk deletion approach (Sykfl/fl; mb1cre-ERT²), Hobeika et al. (2015) now reprobed the importance of Syk in BAFFR-mediated survival signaling and arrive at a somewhat different scenario. It is important to mention that constitutive deletion of Syk not only has a dramatic effect on the reactivity of various hematopoietic lineages (Kiefer et al., 1998; Bohmer et al., 2010) but especially on the nascent B-cell pool, essentially abrogating any B-cell development beyond the immature stage (Cheng et al., 1995; Turner et al., 1995). After having validated the functionality of their deletion approach, Hobeika et al. (2015) first showed that tamoxifen-mediated deletion of Syk had a heterogenic effect on the survival of peripheral B cells. While splenic marginal zone B cells and peritoneal B1 cells were strongly reduced in numbers, transitional B cells were surprisingly unaffected and mature splenic B cells were only reduced to an amount that allowed further analysis of cellular reactivity. These mature Syk−/− remainder B cells turned out to be unable to mobilize Ca²⁺ upon BCR or latrunculin stimulation and exhibited inferior total tyrosine phosphorylation upon pervanadate treatment when compared to controls. Interestingly, these cells were unable to activate mTORC1 and exhibited a reduced potential to migrate toward CXCL12, which is in line with the reported function of Syk in B-cell polarization (Pearce et al., 2011). In contrast, Syk deficiency had no effect on TLR4 (LPS), TLR9 (CpG), IL-4, or CD40 stimulation, showing that these receptors function independently.

In the next step, Hobeika et al. (2015) addressed the potential of Sykfl/++;mb1cre-ERT² B cells to populate Rag2−/−;yc−/− mice, which are void of intrinsic B and T cells under competitive and non-competitive transfer conditions. Even two months post-transfer, a significant portion of Syk-deleted cells persisted in the presence of wild-type competitor B cells, immediately questioning their potential to respond to BAFFR-mediated pro-survival signals. Surprisingly and in noteworthy contrast to Schweighoffer et al. (2013), the authors showed that when cultured in vitro, tamoxifen-induced Sykfl/++;mb1cre-ERT² B cells still retained responsiveness to BAFF. In the presence of BAFF, tamoxifen-induced Sykfl/++;mb1cre-ERT² B cells were only reduced by half in numbers when compared to wild-type control cells and presented with negligible changes in BAFFR expression. To investigate the possibility of a persisting partial dependence on BAFFR signaling in vivo, the authors further treated Sykfl/++;mb1cre-ERT² and control mice with an antibody blocking the interaction of BAFF/BAFFR. In accordance with their in vitro findings, blocking BAFFR with neutralizing antibodies under
Syk null conditions precipitated a comparable reduction in mature follicular B-cell frequencies in vivo, arguing for an actively employed and functional BAFFR-mediated survival route when Syk is not expressed (Fig 1B).

Loss of the BCR mlgM heavy chain leads to the death of B cells, which can be rescued by a constitutively active version of the lipid kinase PI3K (Srinivasan et al., 2009). In a final and laborious approach, Hobeika et al (2015) set out to investigate this previously reported importance of the CD19/PI3K kinase pathway for B-cell homeostasis by crossing Sykfl/fl;mb1cre-ERT2 mice with a combined deficiency on top of that, of an inducibly deletable FoxO1 allele (yielding FoxO1fl/fl;Sykfl/fl;mb1cre-ERT2;CD19−/− mice) restored B-cell numbers to levels of Sykfl/fl;mb1cre-ERT2 mice, the BCR would be unlikely to signal survival via Syk.

The study by Hobeika et al (2015) significantly deepens our insight into the mechanisms ensuring appropriate populations of peripheral B cells. While it provides strong genetic evidence for PI3K-mediated survival signaling from CD19, the origin of the Syk-mediated survival signal in resting B cells remains to be clarified. The long-standing model of stimulation-induced recruitment and activation of Syk to the BCR has recently been supported in a number of elegant studies investigating the nano-composition of the B-cell membrane (reviewed in Maity et al., 2014). Consequently, in resting peripheral B cells, the BCR would be unlikely to signal survival via Syk.

In conclusion, the authors therefore suggest that CD19 indeed boosts B-cell survival via PI3K-mediated degradation of the pro-apoptotic transcription factor FoxO1. In conclusion, the authors therefore suggest synergistic pro-survival functions of BAFFR and CD19 in addition to Syk-mediated survival signals. Here, CD19 signals Akt activation, while BAFFR and Syk signal independently. If Syk signaling under homeostatic conditions involves the BCR or other receptor systems (blue) remains open.

References


