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B cell activating factor (BAFF) and BAFF receptors: fakes and facts

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Summary

Analysis of B cell activating factor (BAFF) receptors before and after B cell depletion therapy (BCDT) might offer a clue to the understanding of whether some B cell subsets may represent useful biomarkers of biological and clinical responses. Among the BAFF receptors in a cohort of rheumatoid arthritis (RA) patients, the AA have shown, by fluorescence activated cell sorter (FACS) analysis of median fluorescence intensity (MFI), that transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) and B cell maturation antigen (BCMA) do not change, whereas the most important, BAFF receptor 3 (BR3), appears to be decreased before as well as after BCDT in all B cell subsets but not in plasmablasts, the most important subset, depleted by BCDT.

Keywords: B cell depletion therapy, BAFF, BAFF receptors, BR3, rheumatoid arthritis

Since its discovery in 1999 by Schneider *et al.* [1], the B cell activating factor (BAFF) molecule arose as a key driver of 'proliferation of anti-immunoglobulin M-stimulated B cells'. It was expressed mainly as a mRNA by naive and activated T cells and monocyte-derived dendritic cells, but not by B cells. Its main receptor, BAFF-R (BR3), was shown to be expressed almost exclusively by B cells, but not by fibroblasts, T cells, epithelial or endothelial cells.

However, 4 years later, Avery *et al.* [2] demonstrated that BAFF enhanced the survival of plasmablasts derived from memory B cells selectively. More importantly, they showed that while CD40L (ligand) induced the proliferation of non-differentiated blasts, BAFF prevented the apoptosis of immunoglobulin (Ig)-secreting cells (ISC), thus increasing Ig synthesis, and this was accompanied by a reduction of the main BR3, while the other receptor, B cell maturation antigen (BCMA), was induced. Therefore, BAFF does not induce proliferation but, in particular, enhances plasmablasts survival.

The BAFF molecule is known to exert its biological effects through three receptors – transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI), BCMA and BAFF-R (BAFF-R/BR3). B cells accumulate in TACI-deficient mice, suggesting that TACI reduces B cell development, and no gross effect on B cell development or antigen-specific immune responses has been observed in BCMA-null mice [3].

These data show clearly that through BR3, BAFF promotes preferentially the survival of $CD38^+$ activated memory B cells and $CD38^+$ rapidly dividing and activated plasmablasts. BR3 signalling promotes the phosphorylation of proximal BCR signalling components, including spleen tyrosine kinase (Syk) and Igα [4], and it has been demonstrated that inducible Syk deletion results in reduced BAFF-dependent B cell survival, despite intact alternative nuclear factor kappa B (NF-κB) signalling [5]. Furthermore BAFF seems to co-opt signalling components of the BCR to promote CD19 phosphorylation, resulting in phosphoinositide 3-kinase (PI3K)-dependent B cell survival [6]. These studies clearly stress the concept that the role of BAFF as an amplifier of the autoimmune response occurs mainly through plasmablast survival and activation.

Consequently, the main driver of an amplified autoimmune loop [7] is BR3, and BAFF levels exert their effects on the B cell subset that plays the major role; namely, the plasmablasts.

This background paves the way to the interpretion of the possible clinical consequences of therapies directed to deplete the B cells ([B cell depletion therapy (BCDT)] in patients with autoimmune diseases, rheumatoid arthritis (RA) [8], systemic lupus erythematosus (SLE) [9], primary Sjögren's syndrome [10] and others. In particular in RA, plasmablasts, along with the double-negative B cells, were shown to be the subsets influenced mainly by BCDT [8]. All the above data suggest that it is very unlikely TACI and

BCMA will display any major change, whereas BR3 expression and the behaviour of double-negative B cells and plasmablasts should be the real targets of studies on the repopulation after BCDT.

Becerra *et al.*, in this issue of *CEI*, investigated the behaviour of the three BAFF receptors before and after BCDT through minimal fluorescence intensity (MFI) and, as expected, found no variation in BCMA expression in B cells before and after therapy, the percentage of TACI expression in repopulating B cells wa lower and BR3 expression cells were also lower than in healthy controls. No data regarding mRNA expression were provided, and unfortunately the characterization of the B cell compartment lacked the CD27 biomarker and relied only upon IgD and CD38. These biases (no mRNA assessment, no careful analysis of the biomarkers) has prevented the proper evaluation of the BAFF receptors in the B cell subsets before and after BCDT.

Despite this, they were able to show that repopulating B cells had a lower expression of BR3, especially the naive B cells, but not the plasmablasts (defined as IgD^{-}, $CD38^{++/+++}$ B cells), and this was especially evident in patients relapsing after 3 months from the infusion of rituximab used as BCDT. As expected, no statistical correlation was found between BR3 expression and BAFF serum levels, nor between BAFF levels and B subsets. Therefore, in RA, BR3–MFI seems to be decreased in naive B cell subsets after BCDT, suggesting that the effects of BAFF should be decreased even during the further developmental steps of the B cells.

Conversely, in Chinese SLE, the detected BR3 protein expression in SLE patients, was reduced in $CD19^{+}IgD^{+}CD27^{-}$, $CD19^{+}IgD^{+}CD27^{+}$ and $CD19^{+}IgD^{-}CD27^{+}$ B cells compared to the counterparts of healthy controls, thus suggesting that the development of B cells was compromised from the naive to the full memory B cell subsets. The same down-regulation of BR3 was seen in primary Sjögren's patients, thus raising the hypothesis that, in at least three autoimmune diseases, BR3 expression is actually down-regulated. Should we target BAFF when BR3 is down-regulated?

Summarizing the take-home messages coming from the analysis by Becerra *et al.*'s study, (a) the MFI expression of BR3 in the B cell pool appears to be of little clinical usefulness to follow the course of RA after BCDT; (b) we still do not know whether or not BR3 expression at the mRNA and MFI levels, in the subsets influenced mainly by BCDT, the double-negative B cells and plasmablasts, is really down-regulated; and (c) the focus of future research should point to full understanding of the potential as biomarkers of BR3 mRNA and MFI, in double-negative B cells and plasmablasts in all autoimmune diseases before BCDT, after BCDT and during relapses or clinical unresponsiveness, and relate this expression to the clinical disease activity.

These data could help to understand more clearly when BAFF should be the target of therapy in these diseases.

Disclosure

The authors declare no conflicts of interest.

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