



# Function, occurrence and inhibition of different forms of BAFF

Mahya Eslami and Pascal Schneider

B cell activating factor (BAFF or BLyS), an important cytokine for B cell survival and humoral immune responses, is targeted in the clinic for the treatment of systemic lupus erythematosus. This review focuses on the structure, function and inhibition profiles of membrane-bound BAFF, soluble BAFF 3-mer and soluble BAFF 60-mer, all of which have distinct properties. BAFF contains a loop region not required for receptor binding but essential for receptor activation via promotion of BAFF-to-BAFF contacts. This loop region additionally allows formation of BAFF 60-mer, in which epitopes of the BAFF inhibitor belimumab are inaccessible. If 60-mer forms in humans, it is predicted to be short-lived and to act locally because adult serum contains a BAFF 60-mer dissociating activity. Cord blood contains elevated levels of BAFF, part of which displays attributes of 60-mer, suggesting a role for this form of BAFF in the development of foetal or neonate B cells.

## Address

Department of Biochemistry, University of Lausanne, Epalinges, Switzerland

Corresponding author: Schneider, Pascal ([pascal.schneider@unil.ch](mailto:pascal.schneider@unil.ch))

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## BAFF, APRIL and their heteromers

BAFF and APRIL (a proliferation-inducing ligand) are related cytokines of the TNF family that are first expressed as type 2 transmembrane proteins and then processed at furin cleavage sites to release soluble cytokines [1]. BAFF and APRIL can also associate as biologically active heteromers in 2:1 or 1:2 ratio. These heteromers were first identified in the serum of patients with rheumatic disease [2]. Both BAFF and APRIL bind to TACI (transmembrane activator and CAML interactor) and B cell maturation antigen (also known as BCMA), while BAFF can additionally bind to BAFFR (BAFF receptor). These receptors are mainly expressed by B

cells and plasma cells at different stages of their development [3–5].

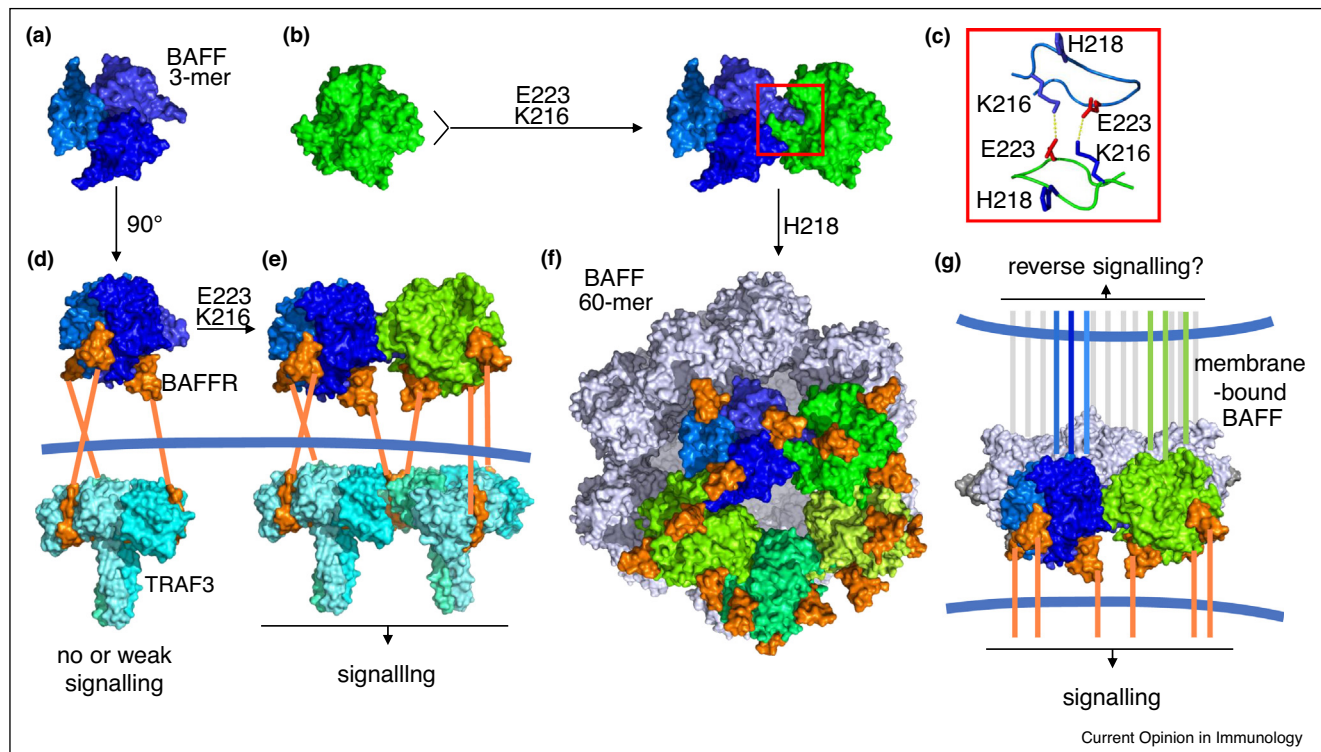
## Three forms of BAFF

BAFF exists in three forms: membrane-bound BAFF, soluble BAFF 3-mer and soluble BAFF 60-mer [6]. Although these forms all bind to receptors, they differ in their levels of functional activity [6]. For example, only multimeric forms of BAFF or APRIL could efficiently activate TACI on primary mouse B cells, a result that was however not observed with human B cells [6,7]. At least one form of BAFF escapes inhibition by a clinical BAFF-targeting drug, making these forms relevant to pharmacology [6]. This review focuses on the biochemistry of different forms of BAFF, on their inhibition profiles by atacicept (a soluble TACI-Ig decoy receptor) and belimumab (a monoclonal anti-BAFF antibody), and on their sizes in human fluids.

## Membrane-bound BAFF

The detection of membrane-bound BAFF expressed by myeloid or stromal cells [8] is not trivial and requires suitable anti-BAFF antibodies. mAbs 9B6, 12D6, and 2E5 stain human monocytes [9–11], but their validation on BAFF-transfected cells has unfortunately not been reported. We mention this because mAb 9B6, obtained from the ATCC (American type culture collection), recognized recombinant BAFF by ELISA but did not stain membrane-bound BAFF in transfected cells or in furin-deficient U937 cells expressing membrane-BAFF detected by other reagents [12] (and PS, personal observations). However, the independently generated mAb 1D6, which was validated to stain BAFF transfected controls by FACS, also stained membrane-bound BAFF by immunohistochemistry on follicular dendritic cells in B cell areas of human lymph nodes [13]. Follicular dendritic cells are not derived from bone marrow cells but are of mesenchymal origin, in line with the observation that BAFF produced by radiation-resistant cells, but not by hematopoietic cells, suffices to sustain normal numbers of follicular and marginal zone B cells in mice [14]. Subsequent studies supported the role of stromal cells, and in particular follicular dendritic cells, in the affinity maturation and activation of B cells [15]. In another study, selective ablation of follicular reticular cells significantly reduced BAFF level in lymph nodes [16]. In addition, BAFF expression by neutrophils and dendritic cells was demonstrated in BAFF reporter mice under resting condition, which was increased upon stimulation. Moreover, T cell-independent antibody response was reduced by BAFF deletion in either of these cells [17].

Figure 1



Three forms of BAFF: 3-mer, 60-mer, and membrane-bound.

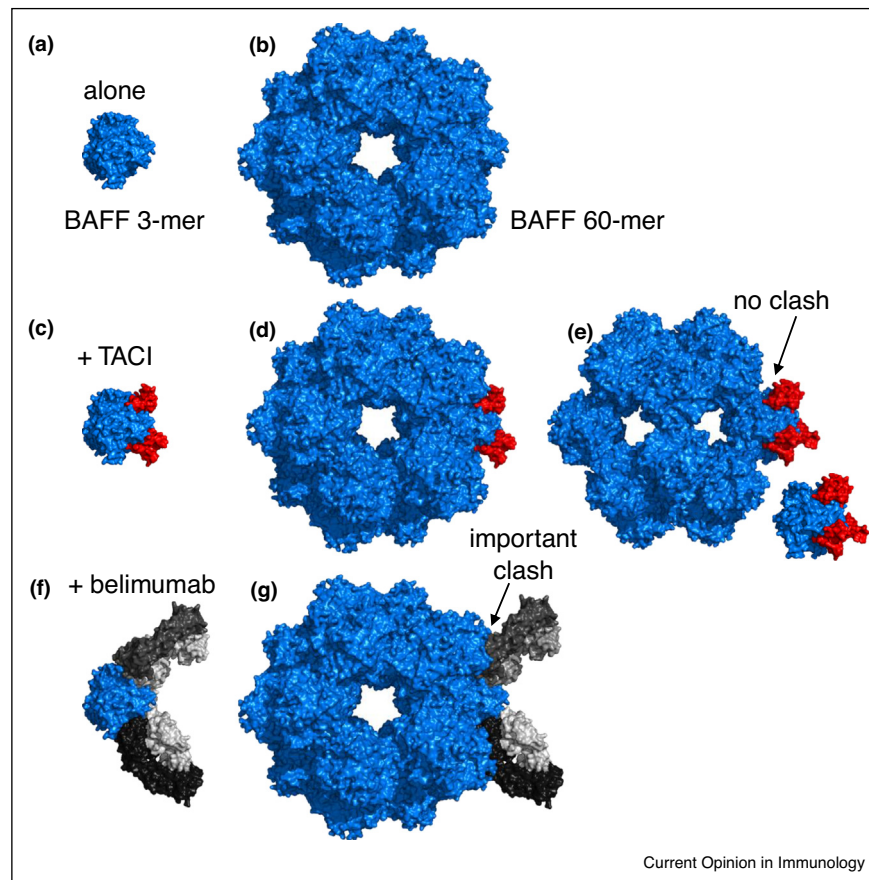
**(a)** Top view of a BAFF 3-mer in an orientation where spurs formed by the flap region are evident. Monomers are shown in shades of blue. **(b)** Two individual 3-mers can hook via the flap region to transiently form 6-mers. This requires amino acid residues E223 and K216 in the flap region. **(c)** Detailed view of the 3-mer to 3-mer interaction shown with a red square in panel (b). E223 and K216 form electrostatic interactions at the core of the interaction, while H218 occupies a more peripheral position. **(d)** Side view of a BAFF 3-mer bound to the transmembrane receptor BAFFR (in orange). The intracellular domain of BAFFR interacts with trimeric TRAF3 (in cyan), a molecule involved in signal transduction. However, soluble BAFF 3-mer transmits no or very low signal in BAFFR-expressing cells, unless **(e)** it can interact via flap-flap interactions with a neighbour BAFF-BAFFR unit. Initiation of signal transduction critically requires E223 and K216, but not H218. **(f)** Twenty soluble BAFF 3-mers can assemble into BAFF 60-mer, which is stable at neutral and basic pH. This critically requires residue H218 in addition to E223 and K216. **(g)** Hypothetical configuration of membrane-bound BAFF, in which two to five 3-mers could hook together via the flap loop to trigger BAFFR activation. Reverse-signalling in BAFF-expressing cells upon binding to receptors remains to be demonstrated. Structures were drawn from protein data base (pdb) coordinates files 1OQE and 1POT for BAFF 60-mer bound to BAFFR, and 2GKW for coiled-coil and TRAF-C domains of TRAF3 bound to an intracellular segment of BAFFR.

The functional importance of membrane-bound BAFF was investigated in mice expressing (almost) uncleavable BAFF with a mutation in the furin cleavage site. Like BAFF-ko mice, uncleavable BAFF mice had only few B cells, highlighting a non-redundant role of soluble BAFF [18]. Treatment of BAFF-ko mice with soluble recombinant BAFF 3-mer restored peripheral B cells and antibody responses, but not CD23-expressing B cells. The latter only reappeared with BAFF 3-mer in the presence of membrane-bound BAFF, or with BAFF 60-mer, suggesting that multimeric forms of BAFF act after BAFF 3-mer, probably at subsequent developmental stages [18].

Membrane-bound BAFF comprises a 46 amino acid residues-long intracellular domain of unknown function, which might be involved in trafficking or in receptor-

induced signals in cells expressing the ligand [19]. The latter function of reverse-signalling has been studied in monocytes and macrophages that were indeed activated by anti-BAFF antibodies or TACI-Fc [20,21]. However, a similar type of study conducted in bone marrow-derived macrophages expressing uncleavable BAFF, or that were deficient for BAFF (*Baff*<sup>-/-</sup>), APRIL (*April*<sup>-/-</sup>) or Fc receptor (*FcRγ*<sup>-/-</sup>) concluded that activation of ERK and Akt by TACI-Fc required neither BAFF nor APRIL, but was dependent on (a) Fc receptors in target cells and (b) Fc aggregates in agonists [22]. In particular, a TACI-Fc engineered not to bind Fc receptors induced no such signals in macrophages. Thus, although reverse-signalling through membrane-bound BAFF might well exist, its study will warrant proper genetic controls to assess specificity.

Figure 2



Belimumab cannot interact with BAFF 60-mer, while TACI can.

(a) Space-filling representations of BAFF 3-mer, (b) BAFF 60-mer, (c) soluble TACI bound to BAFF 3-mer, (d),(e) soluble TACI bound to BAFF 60-mer shown in two different orientations, (f) BAFF 3-mer bound to Fab fragments of the anti-BAFF antibody belimumab and (g) superimposition of BAFF 60-mer with BAFF 3-mer bound to Fab fragments of belimumab showing important clashes between the BAFF 60-mer and the Fab of belimumab that render this interaction impossible, unless BAFF 60-mer dissociates first. Structures were drawn from pdb coordinate files 1OQE for BAFF 3-mer and 60-mer, 1XU1 for TACI CRD2 bound to APRIL (APRIL was overlapped with BAFF to create the models of BAFF-TACI complexes), and 6FXN for 3 Fab fragments of belimumab bound to BAFF 3-mer.

### Soluble BAFF 3-mer and 60-mer

Although little information is available about the structure of membrane-bound BAFF, soluble BAFF was crystallized both as 3-mer and 60-mer (Figure 1). The latter highly active and pH-sensitive BAFF structure is composed of twenty 3-mer regularly hooked in a capsid-like structure via a 10 amino acid-long loop region called the 'flap' [23<sup>•</sup>]. Histidine 218 (H218) in the flap contributes to 60-mer formation, because 60-mer is disrupted by mutation H218A [24<sup>••</sup>]. Membrane-bound BAFF cannot form 60-mer since the neo-N-terminus of BAFF after proteolytic processing is at the inner core of the 60-mer structure. However, membrane-bound BAFF might form 6-mer or even 15-mer in a ring-like structure through flap-flap interactions (Figure 1). Another well-characterized flap mutant, E223K, destroys the electrostatic interaction of glutamic acid 223 with lysine 216 and also prevents 60-mer

formation. Although neither H218-A nor E223K diminished binding to BAFFR, only mutation E223K fully abolished BAFF activity while H218-A did not [24<sup>••</sup>]. This suggests that even in the absence of 60-mer formation (that requires both H218 and E223), the core of the flap region (that requires E223 but not H218) can oligomerize individual BAFF-BAFFR complexes, a critical step for effective signal induction in B cells [24<sup>••</sup>] (Figure 1e). Knock-in mice with mutation E247K (the mouse equivalent of E223K), displayed a B cell phenotype close to BAFF<sup>-/-</sup> mice, despite normal levels of circulating BAFF. Interestingly, treatment of E247K knock-in mice with a cross-linking, non-inhibitory anti-mouse BAFF antibody (5A8), could rescue flap defects in these animals. This indicates that the mere binding of BAFF 3-mer to BAFFR cannot trigger efficient signals unless two or more complexes are assembled via flap-flap interaction.

### Clinical BAFF inhibitors

The implication of BAFF in the pathogenesis of autoimmune diseases is suggested by the elevated level of soluble BAFF measured in the circulation of systemic lupus erythematosus, IgA nephropathy, and Sjögren's syndrome patients [25]. As a result, this cytokine is targeted by blocking agents in autoimmune patients. Belimumab is a recombinant human IgG1 monoclonal antibody that was approved in 2011 as add-on therapy in systemic lupus erythematosus patients [26]. Atacicept consists of the extracellular ligand-binding domain of TACI fused to a modified Fc portion of hIgG1. It was able to efficiently decrease the number of circulating B cells and antibody levels in a phase IIb clinical trial on systemic lupus erythematosus patients [27]. Atacicept can block all three forms of BAFF in addition to APRIL and BAFF-APRIL heteromers (Figure 2). Belimumab blocked the activity of membrane-bound BAFF in furin-deficient U937 monocytic cells less efficiently than atacicept, yet was still able to stain membrane-bound BAFF by FACS [12]. Even more strikingly, belimumab cannot inhibit BAFF 60-mer, because part of its binding epitope is buried by flap-flap interactions that block its access to BAFF 60-mer, while the slimmer TACI portion of atacicept that does not interfere with the flap region can bind and inhibit BAFF 60-mer without dissociating it (Figure 2). Belimumab can however indirectly block BAFF 60-mer by capturing products of spontaneous BAFF 60-mer dissociation and preventing their re-association [24,28]. It is possible that the relatively narrow and selective ligand specificity of belimumab relates to its good safety and tolerance profile in patients [29].

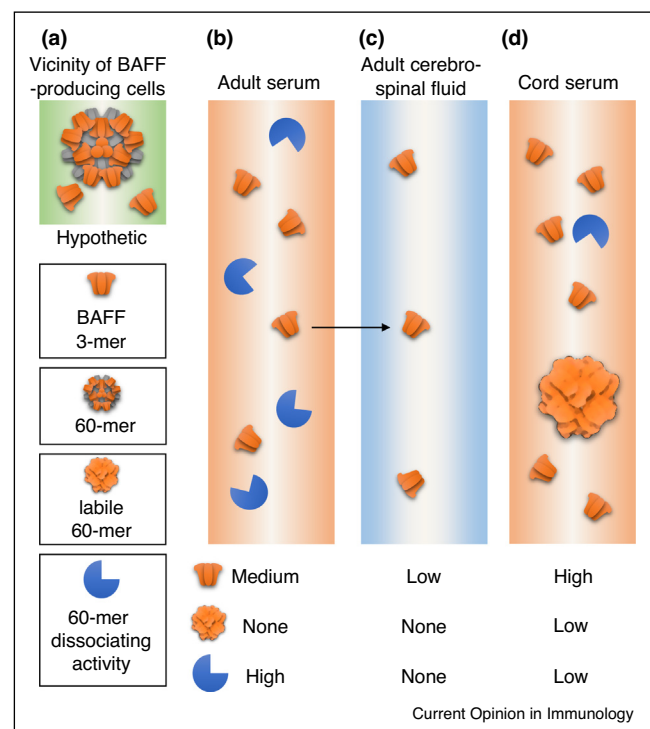
### Soluble BAFF in human fluids

Although it might be important to distinguish soluble forms of BAFF, current measurement methods cannot differentiate them and may even fail to recognize 60-mer. Both 60-mer and 3-mer originate from the naturally processed full-length BAFF expressed in 293T cells, but it is only recently that two distinct sensitive assays have been implemented to identify BAFF 3-mer and 60-mer in primary samples. One is based on the simultaneous use of a) reporter cells that respond better to 60-mer than to 3-mer, and b) selective inhibitors of 3-mer only or 3-mer and 60-mer. The second combines size-fractionation and pH-sensitive detection of 3-mer only or 3-mer + 60-mer by ELISA. Despite the sensitivity of these assays, BAFF was detected exclusively as a 3-mer even in the serum of subjects with common variable immune deficiency (CVID) or *BAFFR*-deficiency who display circulating BAFF levels up to 500-fold higher than controls [30]. Surprisingly, adult human serum contained a BAFF 60-mer-dissociating activity which was neither dependent on physical properties of serum like the pH or salt concentration, nor on soluble receptors, nor on the presence of BAFF-APRIL heteromers (Figure 3). Although the 60-mer inhibitory activity was not observed in the

cerebrospinal fluid of patients with multiple sclerosis, no trace of BAFF 60-mer was identified in these samples, which could be due to the fact that about 80% of the cerebrospinal fluid proteins are derived from blood [31]. However, cord blood that contains about 10-fold higher levels of BAFF compared to adults, also contained milder levels of 60-mer-dissociating activity and consistently (12/12 cord sera) presented up to 10% of a 'labile' form of 60-mer with the size of a 60-mer, a specific activity higher than that of the 3-mer, but that lacked attributes of recombinant BAFF 60-mer such as resistance to inhibition by belimumab [30] (Figure 3).

Previous studies reported the expression of BAFF in the placenta by RT-PCR and also at the protein level [32,33]. In addition, B lineage cells are present in foetal tissues such as the liver, spleen, blood, and placenta. B1 and B2 cells differentiate from hematopoietic stem cells of the

Figure 3



Occurrence of forms of BAFF and BAFF 60-mer dissociating activity in human fluids.

(a) We hypothesize that soluble BAFF 3-mer and 60-mer are released in the vicinity of BAFF-producing cells, although evidence for the production of BAFF 60-mer is currently lacking. (b) Adult human serum contains exclusively BAFF 3-mer unable to reassemble into 60-mer, probably as a result of the high BAFF 60-mer dissociating activity in serum. (c) Cerebrospinal fluids (of patients with multiple sclerosis) contain exclusively BAFF 3-mer despite the absence of 60-mer dissociating activity. This BAFF 3-mer probably originates from the blood. (d) Cord serum contains more BAFF 3-mer than adult serum, low but detectable BAFF 60-mer-dissociating activity, and a high molecular weight form of BAFF of the size of BAFF 60-mer but lacking some other attributes of BAFF 60-mer (labile 60-mer).

neonatal bone marrow or foetal liver. These hematopoietic stem cells are differentiating into B-1 or B-2 common lymphoid progenitors. Later on, B-1 and B-2 progenitor cells give rise to immature surface IgM<sup>+</sup> B-1 and B-2 cells that migrate to the spleen where B-2 cells are developing into transitional and later follicular and marginal zone B cells while B-1 cells generate transitional and afterward B-1a and B-1b cells that migrate to serous cavities [34]. A rtPCR study showed the expression of BAFF, APRIL and their receptors in villous cytotrophoblast and, at higher levels, in mesenchymal cells, two subpopulations of placental cells. These results suggest a function for BAFF and APRIL, and perhaps BAFF 60-mer, in the regulation of human placental B cells [33]. In adults, BAFF 60-mer may (or may not) be produced locally in tissues before dissociation to 3-mer (Figure 3). Genetic models that express WT BAFF or BAFF unable to form 60-mers may shed light on a function of BAFF 60-mer. In this respect, it would be interesting to also monitor the development of B cells in foetuses and new-borns.

### Conclusion and perspectives

The last two decades of study on the biology of BAFF have shed light on the importance of this cytokine in B cell immunology and pathogenesis. Studies aimed at identifying the role of BAFF 60-mer have led to fundamental and in part unexpected findings, namely the crucial role of the flap in signalling, the discovery of a 60-mer-dissociating activity, and the finding of distinct susceptibilities of BAFF 60-mer to clinical inhibitors. However, these studies did not unambiguously clarify the physiological role of BAFF 60-mer, which remains a challenge for future research.

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### Conflict of interest statement

Nothing declared.

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