TACI Deficiency

9

Astrid Bergbreiter and Ulrich Salzer

9.1 Definition

Heterozygous, compound heterozygous, or homozygous alterations in the TNFRSF13B gene are associated with various forms of antibody deficiency including IgA deficiency and common variable immunodeficiency (CVID). These genetic alterations have a low penetrance and are generally not regarded as disease causing, but may be important genetic cofactors affecting especially the T cell-independent antibody responses and increasing risks for autoimmunity and lymphoproliferation. Therefore TACI deficiency is currently viewed as a disease-modifying factor in various forms of antibody deficiency.

9.2 Etiology

The tumor necrosis factor (TNF) superfamily member transmembrane activator and CAML interactor (TACI, encoded by TNFRSF13B) belongs to a group of molecules which regulate B cell homeostasis, differentiation, and function. Its ligands are BAFF (B cell-activating factor, synonyms BLyS, THANK, TALL-1, and zTNF4, encoded by TNFSF13B) and APRIL (a proliferation-inducing ligand, synonyms

A. Bergbreiter
Department of Dermatology, University Hospital Regensburg, Regensburg, Germany
e-mail: Astrid.Bergbreiter@klinik.uni-regensburg.de

U. Salzer (✉)
Department of Rheumatology and Clinical Immunology, Faculty of Medicine, Medical Center—University of Freiburg, Freiburg im Breisgau, Germany

Center for Chronic Immunodeficiency (CCI), Faculty of Medicine, Medical Center—University of Freiburg, Freiburg im Breisgau, Germany
e-mail: ulrich.salzer@uniklinik-freiburg.de

M. M. D'Elios, M. Rizzi (eds.), *Humoral Primary Immunodeficiencies*,
Rare Diseases of the Immune System, https://doi.org/10.1007/978-3-319-91785-6_9

TALL-2 and TRDL-1, protein A, encoded by TNFRSF17), both of which are able to bind to TACI and BCMA (TNFRSF17), whereas BAFFR (BAFF receptor, encoded by TNFRSF13C) is exclusively bound by BAFF only. TACI is able to bind APRIL and BAFF with equally high affinity [1] and serves as the only receptor for BAFF/APRIL heterotrimers [2]. Additionally, both APRIL and its receptor TACI were shown to be capable of interacting with proteoglycans [3, 4]. TACI is a type III transmembrane protein, which contains two cysteine-rich extracellular ligand-binding domains characteristic of members of the TNFR superfamily and shows an expression pattern restricted to lymphocytes (Fig. 9.1).

BAFFR binds BAFF with highest affinity and is expressed on all peripheral B cells from the transitional stage onward except plasmablasts and plasma cells [5]. By interacting with BAFFR, BAFF mediates survival of BAFFR expressing peripheral B cell subsets. In both BAFF and BAFFR knockout mice, severe B cell lymphopenia and humoral immunodeficiency are observed [6, 7]. BCMA expression is confined to terminally differentiated B cells [8, 9] and ensures the survival of long-lived plasma cells in the bone marrow [10]. TACI shows some unique structural features distinct from its closest relatives BCMA and BAFFR. TACI expression varies on distinct B cell subpopulations. In humans, a pronounced expression is found on marginal zone B cells and on CD27+ memory B cell subsets [5, 8, 9]. TACI expression is also more regulated and strongly induced after in vitro treatment with various B cell stimulation agents [11, 12]. TACI has two additional 5′ exons allowing the receptor to be expressed as two splice variants containing either one or

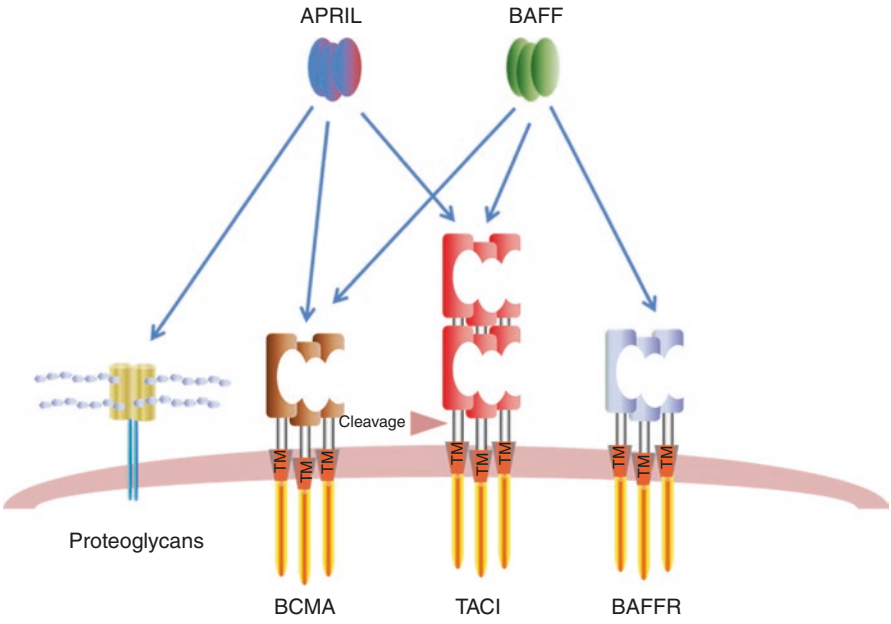

Fig. 9.1 Overview of the family of BAFF/APRIL ligands and receptors

two cysteine-rich extracellular domains, of which only one seems to be functionally relevant [13]. The alternative mRNA splicing of the human TACI gene results in two different main isoforms, the short and long TACI isoforms. Murine B cells and human pre-B cells transduced with the long TACI isoform expressed CD19 and IgG. These cells had less XBP-1 and BLIMP-1 mRNA. Cells transduced with the short TACI isoform became larger and CD138 positive and had more BLIMP-1 and XBP-1 mRNA and morphologically resembled plasma cells. These cells also showed an activation of the classical NFκB pathway and the short TACI protein co-localized with MyD88 and calcium-modulating cyclophilin ligand [14].

Single BAFF or APRIL homotrimers are able to bind TACI, but for efficient signaling ligand multimers are necessary. Soluble BAFF was shown to form 60mers, which are very potent activators of TACI. APRIL can build multimers by binding to heparan sulfate proteoglycans (reviewed in [15]). It was shown that in BAFF and APRIL heteromers, the number of BAFF and APRIL proteins forming the heteromers influences receptor-binding specificities and activities. Trimers consisting of one BAFF and two APRIL proteins bound to TACI and BCMA but not to BAFF receptor, thereby showing similarity to APRIL. Heteromers which consist of two BAFF and one APRIL protein only weakly bind to BAFF-R but preferably bind to TACI and to BCMA. Since heteromers were shown to be less active than BAFF, it was hypothesized that they might reduce BAFF activity in vivo [16]. It was also reported that an endogenous soluble form of the TACI protein was detected in vivo. The soluble protein is released by a disintegrin and metalloproteinase 10 (ADAM 10). The remaining membrane fragment of the protein is cleaved by a gamma-secretase. Soluble TACI can assemble homotypically. By binding BAFF and APRIL, soluble TACI can inhibit B cell survival and NFκB activation. Interestingly, soluble TACI was found in the sera of patients with SLE. The amount of soluble TACI in the serum correlated with disease activity [1]. Similar to TACI, there also exists a soluble form of the BAFF receptor. It is cleaved from the cell surface by ADAM 10 in circulating B cells or by ADAM 17 in germinal center B cells. Shedding of the BAFFR is BAFF dependent and only occurs in cells which co-express TACI [17].

Inside the cell, a binding site for MyD88 is located within the cytoplasmic domain of TACI. Signaling via TACI-MyD88-IRAK1-IRAK4-TRAF6-TAK1 leads to activation of the canonical NFκB pathway [18]. Finally, TACI was originally identified as a CAML interacting receptor [19, 20] and thus is able to signal both via the NFκB and NFAT/AP-1 signaling pathways (Fig. 9.2).

TACI interacts in a ligand-dependent way with activated TLR7 and TLR9 [21]. In vitro studies established APRIL and BAFF as T cell-independent inducers of immunoglobulin class-switch recombination in B cells via TACI [22–24]. In response to APRIL and BAFF, murine naive B cells secrete switched isotypes IgG1 and IgA and switch to IgE with addition of IL-4. This was mediated through both BAFFR and TACI [24]. In this respect the APRIL-TACI interaction is critical for the induction of IgA as APRIL−/− mice show a selective deficiency of this isotype and BAFFR does not bind APRIL [25]. Similarly in humans, BAFF and APRIL mediate class switching toward IgG and IgA in the presence of IL-10 or TGF-β and IgE in the presence of IL-4 [23].

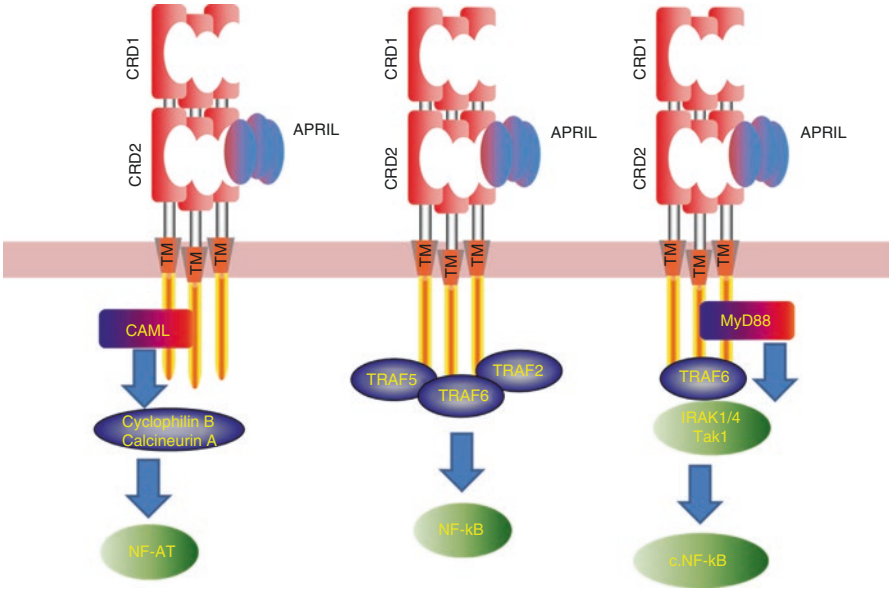

Fig. 9.2 TACI structure, downstream interaction partners, and signaling

The in vivo role of TACI in immune responses has been addressed by several mouse models. Three *tnfrs13b*-deficient mouse strains have been initially generated, which show considerable diversity in their immunological phenotypes [26–28]. Von Bülow et al. demonstrated impaired generation and maintenance of T cell-independent type II responses directed against polysaccharide antigens of encapsulated bacteria like *Streptococcus pneumoniae* in their TACI-deficient mice. Total B cell numbers were elevated, but otherwise B cells developed normally. The architecture of secondary lymphoid organs was normal with intact germinal centers reflecting the unimpaired T cell-dependent antibody responses in the mice [27]. A second TACI knockout mouse reported by Yan et al. [28] confirmed the findings of expansion of peripheral B cells and the impaired T cell-independent type II response; in addition, these second strains of TACI knockout mice had an altered splenic architecture with prominent germinal centers and an increased cellularity of B cell follicles. In vitro B cells were hyperresponsive to mitogenic stimuli resulting in enhanced proliferation and immunoglobulin (Ig) production supporting a role of TACI as a negative regulator [28]. This observation was further confirmed by a third report [26] on a TACI-deficient mouse strain developing a fatal SLE-like disorder. In addition, lymphoma occurred in up to 15% of these TACI−/− mice. Thus in conclusion, the early knockout studies in mice suggested predominantly an inhibitory role for TACI in immune responses. However, the complete knockout of TACI in mice probably does not reflect the human situation, where usually heterozygous point mutations are found. To address this issue, several mouse models carrying the murine equivalents C76R and A144E of the two most frequent amino acid alterations in humans, C104R and A181E, have been generated [29–32]. Interestingly, these four different mouse

strains show again considerable phenotypic differences, which might be attributed to the type of genetic manipulation (transgenic mice on a TACI knockout background versus point mutation knock-in mice) or the different genetic backgrounds. The first two reported mouse strains, expressing either the C76R or the A144E variant in a TACI−/− background, showed reduced serum IgA or IgA and IgM levels as well as impaired type II T cell-independent antibody responses but lacked signs of lymphoproliferation and autoimmunity [30, 31]. The third reported mouse strain, a C76R knock-in mutant expressed under the endogenous TACI promoter, showed hypogammaglobulinemia affecting IgM and IgG1, impaired T cell-independent vaccination responses, and elevated B cell numbers and splenomegaly [32]. The recently reported second A144E mouse model had low IgG, IgA, and IgM and impaired antipneumococcal antibody responses [29], but did not show signs of lymphoproliferation.

9.3 Immunological and Clinical Manifestations of Human TACI Deficiency

Further evidence that TACI positively regulates terminal B cell differentiation came from the discovery that mutations in the TNFRSF13b/TACI gene were associated with CVID in humans [23, 33]. Single nucleotide changes, either missense or nonsense or frameshift, are most common. According to their location and type of mutation, three major groups can be identified (Fig. 9.3). The first group (type I) are missense mutations affecting the ligand-binding domains of TACI. These mutations usually lead to an impairment of ligand binding to the mutated receptor [33, 34]. The

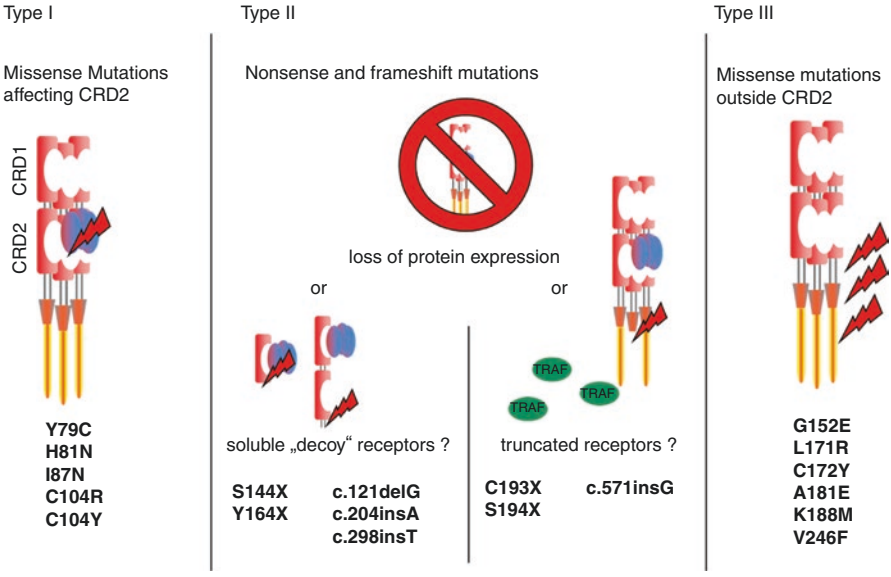

Fig. 9.3 TACI mutation types

most common TACI variant found, C104R, is the prototypical member of this group. The disruption of a disulfide bridge by this mutation causes a complete loss of binding activity in homozygous mutated patients and a 50% loss in heterozygotes [33, 34]. Although an early in vitro study suggested possible dominant-negative effects driven by the mutant C104R allele [35], this could not be confirmed in vivo and by other studies. The type II mutations are frameshift or nonsense mutations, which most likely lead to loss of protein expression, thereby causing haploinsufficiency in the heterozygous state. Interestingly, many patients with Smith-Magenis syndrome (SMS) show a microdeletion at chromosome 17 p11.2. Since the TACI gene is located within this chromosomal region, the effect of only one remaining TACI allele can be studied in these patients. SMS patients with only one TACI allele showed indeed a reduced expression of TACI and impaired B cell activation. These findings support the view that the loss of one TACI allele results in haploinsufficiency [36, 37]. The third group of TACI mutations are missense mutations located outside the ligand-binding domain. The prototypic member of this group is A181E. These mutations cluster around the transmembrane region, and only few mutations are found in the intracellular TACI domain. The exact mutation mechanism for each of these mutations is currently unknown, but for the murine A144E equivalent, it could be recently demonstrated that the mutated protein is unstable resulting in deficient expression, thus causing haploinsufficiency [29].

Contrasting with the expanded and hyperactive B cell phenotype in TACI-deficient mice, peripheral B cells in human TACI deficiency tend to be normal or slightly reduced, with reduced CD27+ memory B cells numbers in most of the patients. Although TACI shows predominant expression on CD27+ memory B cells, the reductions of these cells are not specific for TACI deficiency but are common in CVID [38]. Many TACI-deficient patients show an enlargement of the secondary lymphoid organs, including the spleen, lymph nodes, and tonsils [33, 34]. Some patients with TACI mutations developed non-Hodgkin lymphoma [23, 34]. In this respect human TACI deficiency mirrors the phenotypes of TACI-deficient mouse models as described above. Furthermore, several lines of evidence from studies on human lymphomas point toward an important role of BAFF and its receptors in lymphomagenesis. TACI, BCMA, and BAFF-R are expressed on multiple myeloma cell lines. BAFF is also expressed by multiple myeloma cells and is also found in the bone marrow of patients with multiple myeloma [9]. CLL B cells also express BAFF, BCMA, and TACI. Triggering of the BAFF receptor activates the noncanonical NFκB pathway, and triggering of BCMA and TACI activates the canonical NFκB pathway. Blocking of the canonical NFκB pathway, but not the alternative NFκB pathway, inhibited the proliferation of CLL cells stimulated by BAFF and APRIL [39]. TACI mutations were also found in a limited number of patients with Good's syndrome, which is characterized by a combined immunodeficiency and thymoma. Saenz-Cuesta found one patient in a cohort of six patients with Good's syndrome with a E117G mutation in TACI, and Margraf et al. reported one patient with a potentially disease-causing heterozygous nonsense mutation (p.Lys154Ter), leading to a premature stop codon before the transmembrane domain and therefore probably to a truncated protein [40, 41]. In a Greek study, patients with sarcoidosis were analyzed for TACI variants. Two patients out of

71 patients screened showed TACI variants, R202H and E36L. In patients displaying tonsillar hypertrophy without an infectious cause, the TACI variants I87N and c.204insA were detected [42].

Autoimmune manifestations occur frequently in patients with TACI deficiency. Most common are autoimmune cytopenias, which occur at similar high frequencies as in other primary immunodeficiencies [43]. Some insights regarding the pathomechanism behind the increased rates of autoimmunity come from studies of the BAFF ligand and receptor system in human autoimmune disease and mouse models. Transgenic mice overexpressing BAFF show signs of an SLE-like disease when they age [44, 45]. The fact that elevated BAFF and APRIL levels were found in SLE patients also suggested a role for TACI in autoimmune manifestations in patients with rheumatic diseases [46–47]. One report, however, showed an inverse correlation between the activity of SLE in patients and APRIL serum levels [49]. In the serum of patients with rheumatic diseases—SLE, rheumatic arthritis, polymyositis, and ankylosing spondylitis—elevated levels of APRIL/BAFF heterotrimers were found in comparison with healthy controls, suggesting an influence of ligand oligomers in disease pathology [2, 50]. Since the BAFF/APRIL-TACI axis seemed to be involved in the pathogenesis of SLE, the coding region of TACI was analyzed in 119 patients with SLE, but no disease-associated mutations were detected [51]. It was assumed that survival signals via BAFF-R in the presence of high BAFF levels would lead to survival of autoreactive B cells. High BAFF levels, however, were not found to impair negative B cell selection. They lead to expansion of autoreactive B cells with low affinity from the normal B cell repertoire. Obviously, autoantibody production from innate B cells is the basic mechanism for the development of autoimmunity and uncontrolled B cell survival. On the one hand, TLR7 can upregulate TACI expression [52]; on the other hand, upregulation of TLR7 via BAFF is TACI dependent [53]. TACI activation can lead to autoantibody production. In mice, loss of TACI expression inhibited class-switched autoantibody production [54]. In a SLE mouse model (Nba2.Yaa), TACI deficiency resulted in a reduced disease activity and a reduced development of glomerulonephritis. Mortality of TACI−/− mice was lower compared to the control group, whereas it was higher than within the control in BCMA−/− mice. In mice with TACI and BCMA deficiency, mortality was comparable to TACI−/− mice. APRIL and TACI−/− mice showed a reduced reaction to T cell-independent type II antigens [55]. If only one TACI allele is carrying a mutation, there is an increased risk of developing autoimmune phenomena. Patients carrying one mutated TACI C104R allele showed, compared to individuals carrying two mutated TACI C104R alleles, high serum levels of antinuclear antibodies. Remarkably, central B cell tolerance is disturbed both in individuals with one mutated and with two mutated TACI C104R alleles. In CVID patients, however, peripheral B cell tolerance is impaired, too. Therefore, the defects in central B cell tolerance cannot be compensated [21].

TACI-deficient patients show impaired antibody responses against polysaccharides after vaccination with pneumovax [23], which is similar in TACI-deficient mice [27]. The extent of hypogammaglobulinemia in humans with TACI deficiency is more variable as compared to TACI-deficient mice, which usually show only mild

hypogammaglobulinemia. In humans all the immunoglobulin isotypes may be affected ranging from hypogammaglobulinemia in the majority of affected to agammaglobulinemia [33, 34] and to IgG subclass deficiencies [42] as well as to IgA deficiency [23, 33] in some. Mutations in the TACI gene were also detected in 1–2% of healthy individuals [56], who usually show normal immunoglobulin levels. This led to the assumption that there might be also an advantage for individuals carrying a TACI mutation. TACI-deficient mice produced IgD antibodies for certain antigens. Infections with *Citrobacter rodentium*, being a murine model for human *E. coli* infections, was cleared with higher efficacy in TACI KO mice than in TACI WT mice [57]. It was suggested that TACI deficiency gives an advantage in younger individuals when it is of great importance to deal with enteritis. In our Western lifestyle and with people reaching higher age under good hygienic conditions, the disadvantages of carrying a TACI mutation including the development of CVID, malignancies, or autoimmunity prevails [57]. TACI variants were also found in Swedish patients with wheeze and asthma. It is unknown, however, in which way TACI variants might increase the risk for asthma [58]. TACI also seems to play a role in the pathogenesis of COPD. The synthesis of IgA1 was elevated in COPD lung tissue. TACI, BAFF, APRIL, and IL-6 were stronger expressed in lung tissue and epithelia of COPD patients than in healthy individuals. IgA is upregulated via the IL-6/IL-6 receptor or the BAFF/APRIL/TACI pathway [59].

9.4 Diagnosis and Management

Since TACI mutations are not disease causing, their verification is currently not considered clinically relevant and is reserved to research studies. Expression analysis of TACI protein (e.g., by flow cytometry) is, however, usually not sufficient to diagnose a TACI defect, since many mutations leave protein expression unimpaired and TACI expressing CD27+ memory B cells may only be detected in low numbers in antibody-deficient patients irrespective of their TACI mutation status. Thus confirmation of a TACI mutation should be done by genetic analysis.

The management of CVID patients carrying a TACI mutation does not differ from conventional CVID. However, one should take into account the higher rates of autoimmune and lymphoproliferative complications seen in these individuals.

References

1. Hoffmann FS, Kuhn PH, Laurent SA, Hauck SM, Berer K, Wendlinger SA, Krumbholz M, Khademi M, Olsson T, Dreyling M, Pfister HW, Alexander T, Hiepe F, Kümpfel T, Crawford HC, Wekerle H, Hohlfeld R, Lichtenthaler SF, Meinl E. The immunoregulator soluble TACI is released by ADAM10 and reflects B cell activation in autoimmunity. J Immunol. 2015;194:542–52.
2. Roschke V, Sosnovtseva S, Ward CD, Hong JS, Smith R, Albert V, Stohl W, Baker KP, Ullrich S, Nardelli B, Hilbert DM, Migone TS. BLyS and APRIL form biologically active heterotrimers that are expressed in patients with systemic immune-based rheumatic diseases. J Immunol. 2002;169:4314–21.

3. Bischof D, Elsawa SF, Mantchev G, Yoon J, Michels GE, Nilson A, Sutor SL, Platt JL, Ansell SM, von Bulow G, Bram RJ. Selective activation of TACI by syndecan-2. Blood. 2006;107:3235–42.
4. Ingold K, Zumsteg A, Tardivel A, Huard B, Steiner QG, Cachero TG, Qiang F, Gorelik L, Kalled SL, Acha-Orbea H, Rennert PD, Tschopp J, Schneider P. Identification of proteoglycans as the APRIL-specific binding partners. J Exp Med. 2005;201:1375–83.
5. Ng LG, Sutherland AP, Newton R, Qian F, Cachero TG, Scott ML, Thompson JS, Wheway J, Chtanova T, Groom J, Sutton IJ, Xin C, Tangye SG, Kalled SL, Mackay F, Mackay CR. B cell-activating factor belonging to the TNF family (BAFF)-R is the principal BAFF receptor facilitating BAFF costimulation of circulating T and B cells. J Immunol. 2004;173:807–17.
6. Sasaki Y, Casola S, Kutok JL, Rajewsky K, Schmidt-Supprian M. TNF family member B cell-activating factor (BAFF) receptor-dependent and -independent roles for BAFF in B cell physiology. J Immunol. 2004;173:2245–52.
7. Schneider P, Takatsuka H, Wilson A, Mackay F, Tardivel A, Lens S, Cachero TG, Finke D, Beermann F, Tschopp J. Maturation of marginal zone and follicular B cells requires B cell activating factor of the tumor necrosis factor family and is independent of B cell maturation antigen. J Exp Med. 2001;194:1691–7.
8. Avery DT, Kalled SL, Ellyard JI, Ambrose C, Bixler SA, Thien M, Brink R, Mackay F, Hodgkin PD, Tangye SG. BAFF selectively enhances the survival of plasmablasts generated from human memory B cells. J Clin Invest. 2003;112:286–97.
9. Novak AJ, Darce JR, Arendt BK, Harder B, Henderson K, Kindsvogel W, Gross JA, Greipp PR, Jelinek DF. Expression of BCMA, TACI, and BAFF-R in multiple myeloma: a mechanism for growth and survival. Blood. 2004;103:689–94.
10. O'Connor BP, Raman VS, Erickson LD, Cook WJ, Weaver LK, Ahonen C, Lin LL, Mantchev GT, Bram RJ, Noelle RJ. BCMA is essential for the survival of long-lived bone marrow plasma cells. J Exp Med. 2004;199:91–8.
11. Batten M, Fletcher C, Ng LG, Groom J, Wheway J, Laabi Y, Xin X, Schneider P, Tschopp J, Mackay CR, Mackay F. TNF deficiency fails to protect BAFF transgenic mice against autoimmunity and reveals a predisposition to B cell lymphoma. J Immunol. 2004;172:812–22.
12. Sakurai D, Kanno Y, Hase H, Kojima H, Okumura K, Kobata T. TACI attenuates antibody production costimulated by BAFF-R and CD40. Eur J Immunol. 2007;37:110–8.
13. Hymowitz SG, Patel DR, Wallweber HJ, Runyon S, Yan M, Yin J, Shriver SK, Gordon NC, Pan B, Skelton NJ, Kelley RF, Starovasnik MA. Structures of APRIL-receptor complexes: like BCMA, TACI employs only a single cysteine-rich domain for high affinity ligand binding. J Biol Chem. 2005;280:7218–27.
14. Garcia-Carmona Y, Cols M, Ting AT, Radigan L, Yuk FJ, Zhang L, Cerutti A, Cunningham-Rundles C. Differential induction of plasma cells by isoforms of human TACI. Blood. 2015;125:1749–58.
15. Mackay F, Schneider P. Cracking the BAFF code. Nat Rev Immunol. 2009;9:491–502.
16. Schuepbach-Mallepell S, Das D, Willen L, Vigolo M, Tardivel A, Lebon L, Kowalczyk-Quintas C, Nys J, Smulski C, Zheng TS, Maskos K, Lammens A, Jiang X, Hess H, Tan SL, Schneider P. Stoichiometry of heteromeric BAFF and APRIL cytokines dictates their receptor binding and signaling properties. J Biol Chem. 2015;290:16330–42.
17. Smulski CR, Kury P, Seidel LM, Staiger HS, Edinger AK, Willen L, Seidl M, Hess H, Salzer U, Rolink AG, Rizzi M, Schneider P, Eibel H. BAFF- and TACI-dependent processing of BAFFR by ADAM proteases regulates the survival of B cells. Cell Rep. 2017;18:2189–202.
18. He B, Santamaria R, Xu W, Cols M, Chen K, Puga I, Shan M, Xiong H, Bussel JB, Chiu A, Puel A, Reichenbach J, Marodi L, Döffinger R, Vasconcelos J, Issekutz A, Krause J, Davies G, Li X, Grimbacher B, Plebani A, Meffre E, Picard C, Cunningham-Rundles C, Casanova JL, Cerutti A. The transmembrane activator TACI triggers immunoglobulin class switching by activating B cells through the adaptor MyD88. Nat Immunol. 2010;11:836–45.
19. von Bulow GU, Bram RJ. NF-AT activation induced by a CAML-interacting member of the tumor necrosis factor receptor superfamily. Science. 1997;278:138–41.

20. von Bulow GU, Russell H, Copeland NG, Gilbert DJ, Jenkins NA, Bram RJ. Molecular cloning and functional characterization of murine transmembrane activator and CAML interactor (TACI) with chromosomal localization in human and mouse. Mamm Genome. 2000;11:628–32.
21. Romberg N, Chamberlain N, Saadoun D, Gentile M, Kinnunen T, Ng YS, Virdee M, Menard L, Cantaert T, Morbach H, Rachid R, Martinez-Pomar N, Matamoros N, Geha R, Grimbacher B, Cerutti A, Cunningham-Rundles C, Meffre E. CVID-associated TACI mutations affect autoreactive B cell selection and activation. J Clin Invest. 2013;123:4283–93.
22. Castigli E, Wilson SA, Scott S, Dedeoglu F, Xu S, Lam KP, Bram RJ, Jabara H, Geha RS. TACI and BAFF-R mediate isotype switching in B cells. J Exp Med. 2005;201:35–9.
23. Castigli E, Wilson SA, Garibyan L, Rachid R, Bonilla F, Schneider L, Geha RS. TACI is mutant in common variable immunodeficiency and IgA deficiency. Nat Genet. 2005;37:829–34.
24. Litinskiy MB, Nardelli B, Hilbert DM, He B, Schaffer A, Casali P, Cerutti A. DCs induce CD40-independent immunoglobulin class switching through BLyS and APRIL. Nat Immunol. 2002;3:822–9.
25. Castigli E, Scott S, Dedeoglu F, Bryce P, Jabara H, Bhan AK, Mizoguchi E, Geha RS. Impaired IgA class switching in APRIL-deficient mice. PNAS. 2004;101:3903–8.
26. Seshasayee D, Valdez P, Yan M, Dixit VM, Tumas D, Grewal IS. Loss of TACI causes fatal lymphoproliferation and autoimmunity, establishing TACI as an inhibitory BLyS receptor. Immunity. 2003;18:279–88.
27. von Bulow GU, van Deursen JM, Bram RJ. Regulation of the T-independent humoral response by TACI. Immunity. 2001;14:573–82.
28. Yan M, Wang H, Chan B, Roose-Girma M, Erickson S, Baker T, Tumas D, Grewal IS, Dixit VM. Activation and accumulation of B cells in TACI-deficient mice. Nat Immunol. 2001;2:638–43.
29. Jabara HH, Lee JJ, Janssen E, Ullas S, Liadaki K, Garibyan L, Benson H, Sannikova T, Bram R, Hammarstrom L, Cruz AC, Siegel R, Manis J, Malley R, Geha RS. Heterozygosity for transmembrane activator and calcium modulator ligand interactor A144E causes haploinsufficiency and pneumococcal susceptibility in mice. J Allergy Clin Immunol. 2017;139:1293–1301.e4.
30. Lee JJ, Jabara HH, Garibyan L, Rauter I, Sannikova T, Dillon SR, Bram R, Geha RS. The C104R mutant impairs the function of transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) through haploinsufficiency. J Allergy Clin Immunol. 2010;126:1234–41.e2.
31. Lee JJ, Rauter I, Garibyan L, Ozcan E, Sannikova T, Dillon SR, Cruz AC, Siegel RM, Bram R, Jabara H, Geha RS. The murine equivalent of the A181E TACI mutation associated with common variable immunodeficiency severely impairs B-cell function. Blood. 2009;114:2254–62.
32. Bacchelli C, Buckland KF, Buckridge S, Salzer U, Schneider P, Thrasher AJ, Gaspar HB. The C76R transmembrane activator and calcium modulator cyclophilin ligand interactor mutation disrupts antibody production and B-cell homeostasis in heterozygous and homozygous mice. J Allergy Clin Immunol. 2011;127:1253–9.e13.
33. Salzer U, Chapel HM, Webster AD, Pan-Hammarstrom Q, Schmitt-Graeff A, Schlesier M, Peter HH, Rockstroh JK, Schneider P, Schaffer AA, Hammarstrom L, Grimbacher B. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. Nat Genet. 2005;37:820–8.
34. Salzer U, Bacchelli C, Buckridge S, Pan-Hammarström Q, Jennings S, Lougaris V, Bergbreiter A, Hagena T, Birmelin J, Plebani A, Webster AD, Peter HH, Suez D, Chapel H, McLean-Tooke A, Spickett GP, Anover-Sombke S, Ochs HD, Urschel S, Belohradsky BH, Ugrinovic S, Kumararatne DS, Lawrence TC, Holm AM, Franco JL, Schulze I, Schneider P, Gertz EM, Schäffer AA, Hammarström L, Thrasher AJ, Gaspar HB, Grimbacher B. Relevance of biallelic versus monoallelic TNFRSF13B mutations in distinguishing disease-causing from risk-increasing TNFRSF13B variants in antibody deficiency syndromes. Blood. 2009;113:1967–76.
35. Garibyan L, Lobito AA, Siegel RM, Call ME, Wucherpfennig KW, Geha RS. Dominant-negative effect of the heterozygous C104R TACI mutation in common variable immunodeficiency (CVID). J Clin Invest. 2007;117:1550–7.

36. Chinen J, Martinez-Gallo M, Gu W, Cols M, Cerutti A, Radigan L, Zhang L, Potocki L, Withers M, Lupski JR, Cunningham-Rundles C. Transmembrane activator and CAML interactor (TACI) haploinsufficiency results in B-cell dysfunction in patients with Smith-Magenis syndrome. J Allergy Clin Immunol. 2011;127:1579–86.
37. Romberg N, Virdee M, Chamberlain N, Oe T, Schickel JN, Perkins T, Cantaert T, Rachid R, Rosengren S, Palazzo R, Geha R, Cunningham-Rundles C, Meffre E. TNF receptor superfamily member 13b (TNFRSF13B) hemizygosity reveals transmembrane activator and CAML interactor haploinsufficiency at later stages of B-cell development. J Allergy Clin Immunol. 2015;136:1315–25.
38. Warnatz K, Denz A, Dräger R, Braun M, Groth C, Wolff-Vorbeck G, Eibel H, Schlesier M, Peter HH. Severe deficiency of switched memory B cells (CD27(+)IgM(−)IgD(−)) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood. 2002;99:1544–51.
39. Endo T, Nishio M, Enzler T, Cottam HB, Fukuda T, James DF, Karin M, Kipps TJ. BAFF and APRIL support chronic lymphocytic leukemia B-cell survival through activation of the canonical NF-kappaB pathway. Blood. 2007;109:703–10.
40. Margraf RL, Coonrod EM, Durtschi JD, Augustine NH, Voelkerding KV, Hill HR, Kumánovics A. TACI mutation p.Lys154Ter identified in Good Syndrome. Clin Immunol. 2013;146:10–2.
41. Sáenz-Cuesta M, Martínez-Pomar N, de Gracia J, Echaniz P, Villegas E, Prada A, Otaegui D, Matamoros N, Cuadrado E. TACI mutation in Good's Syndrome: in search of a genetic basis. Clin Immunol. 2012;145:27–30.
42. Speletas M, Salzer U, Florou Z, Petinaki E, Daniil Z, Bardaka F, Gourgoulianis KI, Skoulakis C, Germenis AE. Heterozygous alterations of TNFRSF13B/TACI in tonsillar hypertrophy and sarcoidosis. Clin Dev Immunol. 2013;2013:532437.
43. Fischer A, Provot J, Jais JP, Alcais A, Mahlaoui N, Members of the CEREDIH French PID Study Group. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. J Allergy Clin Immunol. 2017;140:1388–1393.e8.
44. Mackay F, Woodcock SA, Lawton P, Ambrose C, Baetscher M, Schneider P, Tschopp J, Browning JL. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. J Exp Med. 1999;190:1697–710.
45. Khare SD, Sarosi I, Xia XZ, McCabe S, Miner K, Solovyev I, Hawkins N, Kelley M, Chang D, Van G, Ross L, Delaney J, Wang L, Lacey D, Boyle WJ, Hsu H. Severe B cell hyperplasia and autoimmune disease in TALL-1 transgenic mice. Proc Natl Acad Sci U S A. 2000;97:3370–5.
46. Chu VT, Enghard P, Schürer S, Steinhauser G, Rudolph B, Riemekasten G, Berek C. Systemic activation of the immune system induces aberrant BAFF and APRIL expression in B cells in patients with systemic lupus erythematosus. Arthritis Rheum. 2009;60:2083–93.
47. Treamtrakanpon W, Tantivitayakul P, Benjachat T, Somparn P, Kittikowit W, Eiam-ong S, Leelahavanichkul A, Hirankarn N, Avihingsanon Y. APRIL, a proliferation-inducing ligand, as a potential marker of lupus nephritis. Arthritis Res Ther. 2012;14:R252.
48. Becker-Merok A, Nikolaisen C, Nossent HC. B-lymphocyte activating factor in systemic lupus erythematosus and rheumatoid arthritis in relation to autoantibody levels, disease measures and time. Lupus. 2006;15:570–6.
49. Stohl W, Metyas S, Tan SM, Cheema GS, Oamar B, Roschke V, Wu Y, Baker KP, Hilbert DM. Inverse association between circulating APRIL levels and serological and clinical disease activity in patients with systemic lupus erythematosus. Ann Rheum Dis. 2004;63:1096–103.
50. Dillon SR, Harder B, Lewis KB, Moore MD, Liu H, Bukowski TR, Hamacher NB, Lantry MM, Maurer M, Krejsa CM, Ellsworth JL, Pederson S, Elkon KB, Wener MH, Dall'Era M, Gross JA. B-lymphocyte stimulator/a proliferation-inducing ligand heterotrimers are elevated in the sera of patients with autoimmune disease and are neutralized by atacicept and B-cell maturation antigen-immunoglobulin. Arthritis Res Ther. 2010;12:R48.
51. Salzer U, Birmelin J, Bacchelli C, Witte T, Buchegger-Podbielski U, Buckridge S, Rzepka R, Gaspar HB, Thrasher AJ, Schmidt RE, Melchers I, Grimbacher B. Sequence analysis of TNFRSF13b, encoding TACI, in patients with systemic lupus erythematosus. J Clin Immunol. 2007;27:372–7.

52. Groom JR, Fletcher CA, Walters SN, Grey ST, Watt SV, Sweet MJ, Smyth MJ, Mackay CR, Mackay F. BAFF and MyD88 signals promote a lupuslike disease independent of T cells. J Exp Med. 2007;204:1959–71.
53. Figgett WA, Fairfax K, Vincent FB, Le Page MA, Katik I, Deliyanti D, Quah PS, Verma P, Grumont R, Gerondakis S, Hertzog P, O'Reilly LA, Strasser A, Mackay F. The TACI receptor regulates T-cell-independent marginal zone B cell responses through innate activation-induced cell death. Immunity. 2013;39:573–83.
54. Figgett WA, Deliyanti D, Fairfax KA, Quah PS, Wilkinson-Berka JL, Mackay F. Deleting the BAFF receptor TACI protects against systemic lupus erythematosus without extensive reduction of B cell numbers. J Autoimmun. 2015;61:9–16.
55. Tran NL, Schneider P, Santiago-Raber ML. TACI-dependent APRIL signaling maintains autoreactive B cells in a mouse model of systemic lupus erythematosus. Eur J Immunol. 2017;47:713–23.
56. Pan-Hammarström Q, Salzer U, Du L, Björkander J, Cunningham-Rundles C, Nelson DL, Bacchelli C, Gaspar HB, Offer S, Behrens TW, Grimbacher B, Hammarström L. Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. Nat Genet. 2007;39:429–30.
57. Tsuji S, Stein L, Kamada N, Nuñez G, Bram R, Vallance BA, Sousa AE, Platt JL, Cascalho M. TACI deficiency enhances antibody avidity and clearance of an intestinal pathogen. J Clin Invest. 2014;124:4857–66.
58. Janzi M, Melén E, Kull I, Wickman M, Hammarström L. Rare mutations in TNFRSF13B increase the risk of asthma symptoms in Swedish children. Genes Immun. 2012;13:59–65.
59. Ladjemi MZ, Lecocq M, Weynand B, Bowen H, Gould HJ, Van Snick J, Detry B, Pilette C. Increased IgA production by B-cells in COPD via lung epithelial interleukin-6 and TACI pathways. Eur Respir J. 2015;45:980–93.