

Transmembrane activator and calcium-modulator and cyclophilin ligand interactor mutations in common variable immunodeficiency

John J. Lee*, Esra Ozcan*, Ingrid Rauter* and Raif S. Geha*

Division of Immunology, Children's Hospital and
Department of Pediatrics, Harvard Medical School,
Boston, Massachusetts, USA

Correspondence to Raif S. Geha, Division of
Immunology, Children's Hospital, One Blackfan Circle,
Boston, MA 02115, USA
Fax: +1 617 730 0528;
e-mail: raif.geha@childrens.harvard.edu

* John J. Lee, Esra Ozcan, Ingrid Rauter, and Raif S.
Geha equally contributed to the writing of this article.

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Purpose of review

TNFRSF13B, the gene which encodes transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), is mutated in nearly 10% of patients with common variable immune deficiency (CVID), an antibody deficiency syndrome characterized by loss of memory B cells and plasma cells. This review discusses the normal function of TACI and the role of TACI mutants in CVID.

Recent findings

TACI activates isotype switching, mediates immunoglobulin production in response to type II T-independent antigens, and plays an inhibitory role in B cell homeostasis. Recent evidence indicates that TACI synergizes with CD40 and Toll-like receptors for immunoglobulin secretion and promotion of plasma cell differentiation. The two most common TACI mutants associated with CVID – C104R and A181E – are primarily found as heterozygous mutations suggesting that they either cause haploinsufficiency or exert a dominant negative effect. TACI mutations in CVID are associated with an increased susceptibility to autoimmunity and lymphoproliferation.

Summary

TACI has a dual function in promoting B cell antibody responses and inhibiting B cell proliferation. The observation that TACI mutations are present in healthy participants suggests that modifier genes may play an important role in the development of CVID. The discovery of these genes will help understand the pathogenesis of this disease.

Keywords

autoimmunity, B cells, common variable immune deficiency, lymphoproliferation, transmembrane activator and calcium-modulator and cyclophilin ligand interactor

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Introduction

Common variable immune deficiency (CVID) is the most prevalent human primary immunodeficiency requiring medical attention, with an estimated prevalence of 1 in 25 000 [1,2]. It is characterized by recurrent sinopulmonary infections, particularly with encapsulated bacteria. CVID is complicated by autoimmune manifestations in up to 20% of affected individuals and lymphoproliferation or splenomegaly in approximately one-third of patients [3,4]. CVID is diagnosed on the basis of an impaired ability to produce specific antibodies after vaccination or natural exposure, markedly reduced serum levels of IgG, IgA, and frequently, IgM and exclusion of other causes for antibody deficiency. Most cases of CVID are sporadic, but about 10% are familial, with a predominance of autosomal dominant over autosomal recessive inheritance [5].

The complexity and heterogeneous nature of CVID presents a challenge in understanding the molecular

mechanisms underlying this disease. B cells of CVID patients can be impaired in their ability to undergo somatic hypermutation, to differentiate into memory B cells (both unswitched IgM+CD27+ and switched IgM–CD27+ cells) and plasma cells, or to become activated after antigen receptor crosslinking [3,6–8]. Defects in T cell signaling, lymphoproliferative responses, and cytokine expression have also been described [9]. Despite this heterogeneity, progress has been made in understanding the genetic causes of CVID. A large deletion in inducible costimulator (ICOS) has been described in a group of CVID patients with a common ancestry that impairs T–B cell cooperation [10]. More recently, mutations in CD19 were found in a handful of patients with CVID [11]. These two monogenic causes, however, account for only a very small fraction (<1%) of the CVID population.

Our group and that of Grimbacher's identified mutations in *TNFRSF13B*, the gene encoding transmembrane

activator and calcium-modulator and cyclophilin ligand (CAML) interactor (TACI), that are highly associated with CVID [12,13]. Population studies have demonstrated TACI mutations in 8–10% of the CVID patients [12,13]. Two coding variants, C104R and A181E, are highly represented, accounting for more than 90% of TACI mutations. C104R and A181E, however, are also seen in healthy individuals albeit at a significantly lower frequency. In this review, we will discuss the normal role of TACI in B cell function and consider the effects of TACI mutations in CVID.

TACI structure and signaling

TACI belongs to the tumor necrosis factor receptor (TNF-R) superfamily and is primarily expressed as a type III transmembrane protein [14]. The extracellular region possesses two cysteine-rich domains (CRDs), characteristic of TNF-Rs (Fig. 1). The first CRD drives the assembly of TACI, independent of ligand interaction, into trimers or higher order multimers [15**]. The second CRD governs the binding of TNF ligands, B cell-activating factor of the TNF family (BAFF), and a proliferating inducing ligand (APRIL) to TACI. The intracellular domain of TACI recruits signaling proteins that include

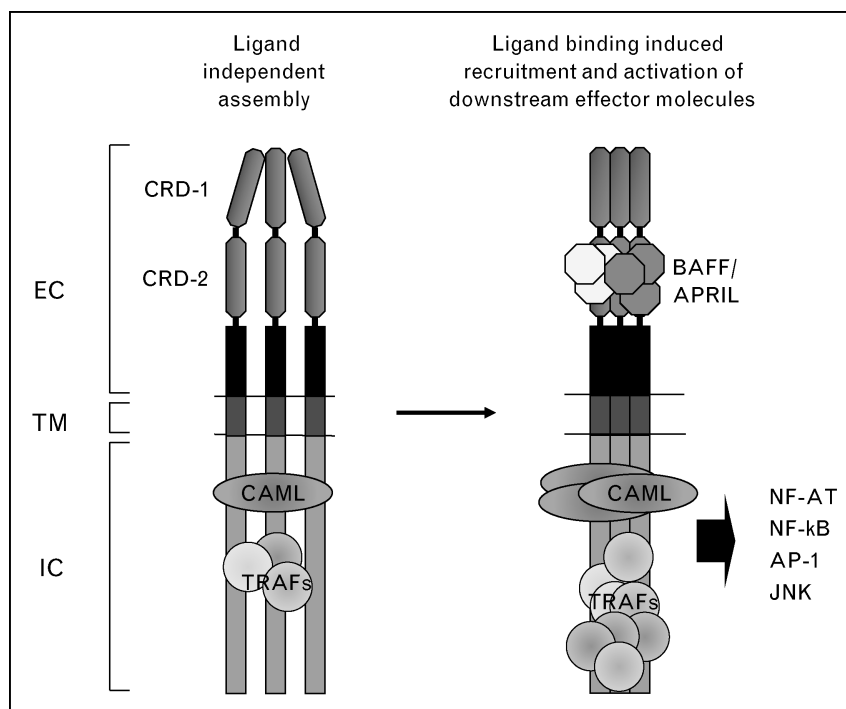
TNF-R-associated factors (TRAFs) and CAML [16,17]. In humans, two splice variants have been described: one that lacks CRD1 [18] and another that encodes for a soluble form of TACI [14].

TACI, like BAFF-R and B cell maturation antigen (BCMA), interacts with TRAF proteins, but only TACI can bind CAML, which is expressed on the surface of cytoplasmic vesicles. TACI ligation may further promote the association of TACI with TRAFs and CAML. TACI activates NF- κ B via the IkappaB kinase (IKK)- γ mediated canonical NF- κ B1 pathway; this is most likely mediated by TRAF proteins [19,20]. TACI can also activate the transcription factor nuclear factor of activated T cells (NF-AT) via CAML, which controls the release of calcium from intracellular stores [17]. In addition, TACI induces the activation of c-Jun NH2-terminal kinase and of the transcription factor AP-1 [17].

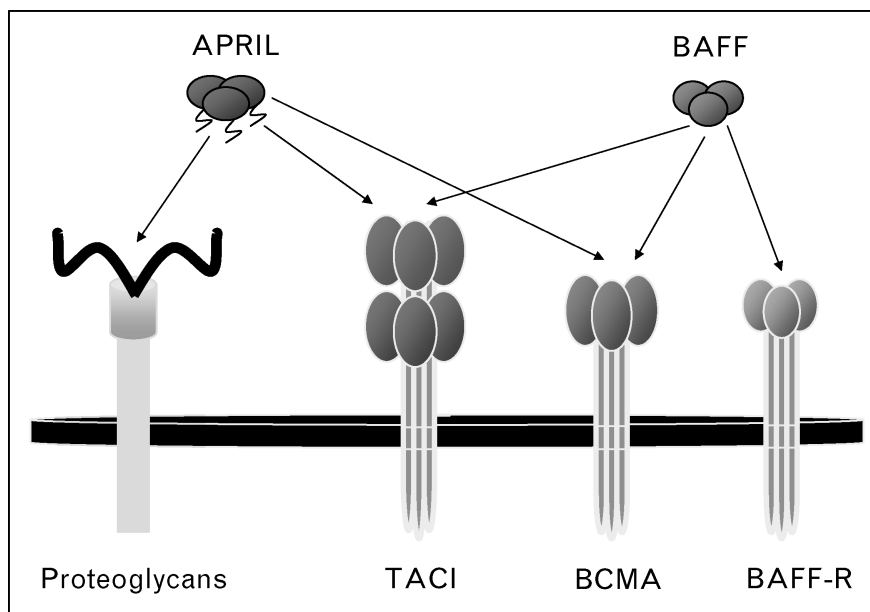
TACI ligands and their receptors

TACI participates in a complex system of ligands and receptors that display overlapping binding specificities (Fig. 2). TACI has two ligands that belong to the TNF

Figure 1 Proposed model of TACI structure and signaling



TACI preassembles via the CRD1 domain prior to ligand binding. Binding of the ligands APRIL and BAFF via CRD2 induces a conformational change strengthening the association with CAML and TRAFs and activating downstream effectors. APRIL, a proliferating inducing ligand; BAFF, B cell-activating factor of the TNF family; CAML, calcium-modulator and cyclophilin ligand; CRD, cysteine-rich domain; EC, extracellular domain; IC, intracellular domain; TACI, transmembrane activator and calcium-modulator and cyclophilin ligand interactor; TM, transmembrane domain; TRAF, TNF-R-associated factor.

Figure 2 TACI ligands and their receptors

The receptors are shown to exist preassembled as trimers for illustrative purposes only. BAFF and APRIL are known to exist as trimers. BAFF also exists as a 60-mer [19]. APRIL, a proliferating inducing ligand; BAFF, B cell-activating factor of the TNF family.

family – BAFF and APRIL – which are expressed as type II transmembrane proteins and can be proteolytically cleaved and secreted [21]. BAFF is expressed mainly by neutrophils, monocytes, macrophages, and dendritic cells. APRIL is expressed in a large variety of tissues that include monocytes, macrophages, dendritic cells, and activated T cells [22]. In addition to TACI, APRIL binds to BCMA and to heparan-sulfated proteoglycans [23,24], whereas BAFF binds to TACI and BCMA as well to its own unique receptor, BAFF-R. Resting B cells express BAFF-R and low amounts of TACI, but no detectable BCMA. B cell activation results in up-regulation of TACI and down-regulation of BAFF-R, followed by delayed BCMA surface expression [25–27]. Increased TACI expression is seen in marginal zone B cells and a subset of activated CD27+ cells [27,28]. TACI expression has been described in activated T cells, monocytes, and dendritic cells [17,29,30]. In addition to the above interactions TACI can be activated by the proteoglycan, syndecan-2 [31].

Role of TACI in B cell activation and differentiation

A number of observations support the central role of TACI in B cell activation and differentiation into plasma cells. It was reported that TACI^{-/-} B cells hyperproliferate to BAFF suggesting that TACI can deliver an antiproliferative signal [32], although this was not seen in another study [33]. APRIL causes modest proliferation of normal B cells (our unpublished obser-

vations). This is dependent on TACI because this effect is not observed using B cells from TACI^{-/-} mice. In addition, class switch recombination and subsequent isotype switching can occur in naïve B cells in response to APRIL and BAFF in a pathway independent of CD40 [34,35]. The magnitude of isotype switching induced by BAFF or APRIL is substantially smaller than that induced by CD40 ligation. TACI is the sole mediator of class switching induced by APRIL, whereas BAFF class switching is mediated by TACI and to a lesser extent by BAFF-R. Switching to IgA appears to be exclusively dependent on TACI as both TACI and APRIL-deficient mice have decreased levels of serum IgA [33,36,37].

In addition, TACI ligation drives plasmablast generation and immunoglobulin secretion in CD40 and Toll-like receptor (TLR) 4 ligand stimulated cultures ([38] and our unpublished observations). A number of recent studies have demonstrated that TLR ligation can up-regulate expression of TACI in B cells [39,40] and expression of its ligands BAFF and APRIL in dendritic cells and B cells [41,42]. This up-regulation of TACI and its ligands by TLR ligands links innate immunity to TACI-mediated activation of B cells and is likely to play a central role in the synergy between TACI and TLRs in B cell activation.

The role of TACI in B cell function *in vivo* has been elucidated by the study of TACI^{-/-} mice. These mice have normal B cell development, but are IgA-deficient

and are impaired in their ability to mount an antibody response to thymus-independent type II (TI II) antigens – an important class of antigens that include TNP-ficoll and pneumococcal polysaccharides [32,33]. This is associated with impaired generation of TI II-specific plasma cells in these mice [43[•]]. The TI II response is also impaired in APRIL-deficient mice [44], but intact in BAFF-R-deficient and BCMA-deficient mice [35,45].

TACI may also participate in the rapid containment of invasive pneumococcal infections. Splenic marginal zone cells, which mediate the early response to pneumococcal polysaccharides, have elevated surface expression of TACI and can interact with dendritic cells that express TACI ligands [22,46]. Furthermore, B cells from newborn mice express low levels of TACI and B cells from human neonates have a modest, although not significant, decrease in TACI expression [47[•],48]. This decreased TACI expression may underline the poor ability of newborns to mount a good antibody response to pneumococcal polysaccharides.

TACI and B cell homeostasis

Given the part TACI plays in promoting humoral immune responses, it has an unanticipated role as a negative regulator in B cell homeostasis. The first indication of this function was observed in TACI-deficient mice that exhibited a marked increase in circulating B cell numbers accompanied by splenomegaly [32,33]. Studies have suggested TACI may deliver pro-apoptotic signals [49], although other studies have described an opposing role for TACI in preventing apoptosis [50]. Presumably as a consequence of this dysregulation of B cell homeostasis, TACI-deficient mice experience an increase in lymphomas and autoimmune phenomenon including lupus-like condition with production of autoantibodies and glomerulonephritis [49]. An alternative explanation for the autoimmunity and B cell lymphoproliferation is that TACI may compete with BAFF-R for BAFF binding, thus limiting BAFF-R mediated B cell survival. In the absence of TACI, an increase in BAFF-R signaling would result in B cell hyperproliferation and activation of autoreactive B cells.

TACI mutations and common variable immune deficiency

A number of TACI mutations have been described in patients with CVID. Table 1 summarizes the mutations we have observed in our clinic. The two most common mutations are C104R and A181E. Each is found in 4–5% of CVID patients and in both sporadic and familial cases. The vast majority of patients with these two mutations are heterozygous, but rare homozygous cases have been identified. Healthy controls have also been found with

Table 1 TNFRSF13B Sequence variants^a

Sequence variant	a.a. change
Significantly associated with CVID	
310T>C	C104R
542C>A	A181E
Uncertain association with CVID ^b	
277_231del	G76fsX3
509G>A	C170Y
512T>G	L171R
204insA	L69fsX11
444C>A (–13aa)	S144X
594C>A, 595C>A	S194X
260T>A	I87N
563A>T	K188M
Not significantly associated with CVID	
215G>A	R72H
602G>A	R202H
659T>C	V220A
752C>T	P251L

^aTable lists sequence variants observed in *TNFRSF13B*; silent mutations are not shown.

^bSignificance undetermined because of low frequency of mutation in CVID population, and absence in healthy controls studied to date.

the C104R and A181E mutations in a heterozygous state, each with an allelic frequency of approximately 0.5%; however, these mutants still have a highly significant association ($P < 0.0001$) with CVID [51^{••},52^{••}]. A number of rare TACI mutations with unclear significance have also been seen in CVID patients, but not in healthy participants to date, for example G76fsX3, C170Y, and L171R. Other mutations, for example R72H, R202H, V220A, and P251L, have a similar frequency in patients and controls. Although early analysis suggested an association of selective IgA deficiency with TACI mutations [12], further studies did not reveal an increase in the incidence compared to controls [51^{••},52^{••}].

Effect of TACI mutations on B cell function

A careful evaluation of the role of TACI mutations in CVID requires an understanding of how a TACI mutation may affect B cell function. Because most CVID patients with TACI mutations are heterozygotes, the impact of the mutant allele on the function of wild-type TACI should also be assessed, namely, does the mutant exert a dominant negative effect or does it simply result in haploinsufficiency? A third possibility is that CVID patients heterozygous for TACI mutations may preferentially express the dysfunctional allele.

The C104R mutation occurs in CRD2 and abrogates binding to BAFF and APRIL [12,13]. In our initial studies we reported that the association of this mutant with wild-type TACI on the cell surface did not interfere with ligand binding, but inhibited ligand-induced NF- κ B activation, suggesting that C104R exerts a dominant negative effect [15^{••}]. However, further experiments and in-vitro and in-vivo analysis of transgenic mice that co-express both wild-type TACI and C76R TACI

(murine equivalent to human C104R) suggest that C104R exerts its effect via haploinsufficiency (unpublished observations).

The A181E mutation substitutes a neutral alanine in the transmembrane domain with a negatively charged glutamine. The mutant can bind ligand normally and associate with wild-type TACI on the cell surface, but is incapable of activating NF- κ B or NF-AT following ligand binding (our unpublished observations). The introduction of a negative charge in the transmembrane domain of the mutant may prevent downstream signaling by interfering with ligand-induced conformational changes of TACI mutimers. We have established a transgenic mouse line homozygous for the murine equivalent of the A181E TACI mutation. Our preliminary analysis indicates that the mutation causes an immune phenotype similar to that of TACI knockout mice notably with impaired responses to TI type II antigens (unpublished data). The effect of the mutant on the function of wild-type TACI remains to be investigated.

The effect of heterozygous C104R and A181E TACI mutations on B cell function in patients with CVID is still under debate. Although there is a consensus that B cell responses to TACI ligation are significantly impaired in CVID patients with TACI mutations, it needs to be further investigated whether these defects are specific to these patients or are part of a generalized impairment of B cell activation that has been observed in the CVID population in response to TACI, CD40, and TLR9 ligands [53,54^{••}].

Two key observations suggest that mutations that affect TACI function, such as C104R and A181E, may not be sufficient by themselves to cause CVID. First, the phenotype in TACI^{-/-} mice only partially parallels CVID. Although the mice are IgA-deficient and prone to autoimmunity and B cell hyperproliferation, they have normal levels of serum IgG and intact Ab responses to T cell-dependent (TD) antigens [32,33]. One important distinction between TACI^{-/-} murine models and TACI mutants found in CVID is that most human mutations do not result in absent protein expression; therefore it could be argued there may be additional effects of these mutations that extend beyond the loss of TACI function. Our preliminary data, however, show that expression of the murine equivalents of C104R and A181E on the TACI null background still does not lead to IgG deficiency (unpublished observations). The second observation is that TACI C104R and A181E heterozygous mutations are present in up to 1% of the general population. It is unlikely that even a fraction of these 'normal' individuals will develop immune deficiency later in life; otherwise, the frequency of CVID would be much higher. Given these observations, other genes

and/or environmental factors are probably needed for TACI mutations to result CVID. Genes along the CD40-CD40L or the TLR pathways may be potential candidates, as it is known that defects in CD40L expression, CD40 signaling, and TLR9 can occur in CVID [53,54^{••},55,56] and that TACI participates in cross-talk with CD40 and TLRs [38[•],39^{••},40,41].

TACI mutations, B cell lymphoproliferation, and autoimmunity

A study evaluating the effect of TACI mutants on lymphoproliferation and autoimmunity found that CVID patients with TACI mutations developed splenomegaly and autoimmune phenomena more frequently than those without TACI mutations [54^{••}]. Elevated serum BAFF levels are not likely to account for this difference, as CVID patients with and without TACI mutations have similar increases in this cytokine [57]. Instead, an intrinsic predisposition for human B cells with TACI mutations to hyperproliferate may account for these findings, similar to observations made in TACI^{-/-} mice. Furthermore, lymphoproliferation may not be limited to the B cell compartment; a polyclonal CD8⁺ lymphoproliferation has been described in a CVID patient heterozygous for C104R TACI mutation [58]. It is also important to note that several patients with the A181E mutation have virtually no circulating B cells (unpublished observations).

Conclusion

TACI is proving to be a receptor that exerts complex effects on B cells. TACI mediates isotype switching, promotes plasma cell differentiation, and is essential for type II TI antibody responses, yet also has an inhibitory role in B cell homeostasis. TACI mutations are significantly associated with CVID, but also can be found in healthy individuals [52^{••}], and thus may need to cooperate with genetic and/or environmental factors to result in CVID. Elucidation of these factors will be critical for understanding the pathogenesis of CVID.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 593).

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