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TACI, isotype switching, CVID and IgAD

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Abstract Common Variable Immunodeficiency (CVID) is the most prevalent human primary immunodeficiency requiring medical attention. Until recently the only known genetic defect specific to CVID was ICOS deficiency that accounts for about 1% of the patients analyzed. Mutations in the TNFR family member TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor), which mediates isotype switching in B cells, were found to be present in 5% of patients with CVID. Mutations in TACI were also found in relatives of patients with CVID who suffered from IgA deficiency (IgAD) as well as in a patient with isolated IgAD. In the majority of patients described to date only one TACI allele is mutated, showing an autosomal dominant transmission of the disease. B cells from individuals with TACI mutations did not produce IgG and IgA in response to the TACI ligand, APRIL (a proliferation-inducing ligand), probably reflecting impaired isotype switching. These results suggest that TACI mutations can lead to CVID.

Keywords TACI · APRIL · BAFF · Isotype switching · Immunodeficiency · CVID and IgAD

APRIL, BAFF and their receptors

The TNF family members APRIL (a proliferation-inducing ligand) and BAFF (B-cell activating factor of the TNF family) both bind to two receptors, BCMA (B cell maturation antigen) and TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor), which are members of the TNF-R family [1]. BCMA is exclusively expressed on B cells, whereas TACI is expressed on B cells and activated T cells. A third

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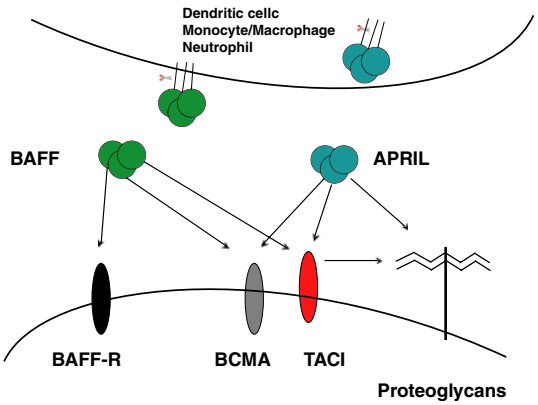

Fig. 1 BAFF, APRIL and their receptors

receptor, BAFF-R that is unique for BAFF is expressed mainly on B cells, but also on resting T cells [2] (Fig. 1). In addition, TACI [3] and APRIL, but not BAFF, bind to proteoglycans on the cell surface, including syndecan-1 (CD138), which is highly expressed on plasma cells. This binding is thought to be important for the multimerization of APRIL [4, 5].

APRIL and BAFF share several features. They: (i) are members of the TNF family of ligands; (ii) are synthesized as type II transmembrane protein with a TNF homology C terminal domain; (iii) are expressed in monocytes/macrophages, dendritic cells and neutrophils [6, 7]; and (iv) are proteolytically cleaved into a soluble form at a multibasic motif by a furin-like protease [8].

BAFF enhances B cell survival. Mice deficient in BAFF have a severe block in B cell development [9, 10], very low levels of serum Igs and impaired specific response to TD and TI (T-independent) antigens. APRIL has no detectable effect on B cell survival. We have shown that APRIL deficient mice have normal B cell numbers, but their serum IgA levels are diminished and they have impaired IgA antibody response to oral immunization with TD antigens and to TI antigens [11].

TACI is expressed on B cells and activated T cells [12]. $TACI^{-/-}$ mice have enlarged spleens and lymph nodes with increased cellularity and increased number of B cells. In addition, $TACI^{-/-}$ B cells showed an increased proliferation rate and increased Ig production in vitro. Despite this in vitro B cell hyperactivity, in vivo the serum IgA and IgM levels are low in these mice and they mount a deficient antibody response to the Type II TI antigens, Pneumovax, and NP-Ficoll. With age, these mice developed autoantibodies with immune complex glomerulonephritis and developed B cell lymphoproliferation. There was in vitro evidence for decreased apoptosis in the B cells of $TACI^{-/-}$ mice suggesting that TACI normally delivers an apoptotic signal to B cells and is a regulator of B cell homeostasis [13–15].

The human TACI gene locus is located on the short arm of chromosome 17, which is a common target for mutation and rearrangement. The TACI extracellular N-terminal domain is characterized by two ''cysteine-rich domains'' (CRDs) that are the hallmark of the TNFR superfamily. The first TACI CRD extends from amino acid (aa) 32 to aa 67, which is missing in an isoform of TACI. The second extends from aa 68 to aa 106 and binds APRIL and BAFF with high affinity [16] (Fig. 2). The CRDs contain a conserved

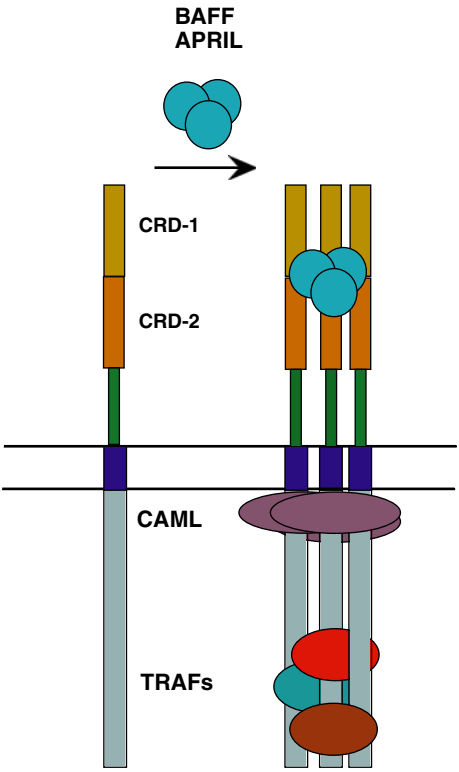

Fig. 2 Structure of TACI and its ligand-dependent recruitment of intracellular signaling molecules

six-residue sequence, (F/Y/W)-D-x-L-(V/T)-(R/G), that is required for APRIL and BAFF binding. TACI, like CD40, recruits TRAF (TNFR associated factor) 2, 3, 5 and 6 and induces NF-kB activation [17, 18]. In addition, TACI induces activation of c-Jun NH2-terminal kinase (JNK) and AP-1. Binding of TRAF2 and/or TRAF3 is essential for CD40 mediated activation of NFkB and JNK and more importantly for CSR [19, 20] while TRAF6 is important in plasma cell differentiation [21]. TACI uniquely interacts with CAML (calcium modulating cyclophilin ligand) that positively regulates the activation of the calcium-dependent phosphatase calcineurin, which dephosphorylates and activates NF-AT (nuclear factor of activated T cells) [12, 22].

BCMA is poorly expressed on resting B cells, but is upregulated on plasma cells and on germinal center B cells [23]. BCMA$^{-/-}$ mice have normal phenotype although plasma cell survival may be somewhat impaired [24]. BCMA plays no detectable role in isotype switching by BAFF and APRIL [25]. The human BCMA gene is on chromosome 16.

BAFF-R is expressed on resting B and T cells. It is downregulated on plasma cells. BAFF-R deficient mice are similar but less severely compromised in their immunophenotype than BAFF$^{-/-}$ mice, as they are still able to mount antibody responses against TI antigens, indicating that these may be mediated by TACI [26, 27]. BAFF-R mediates in part isotype switching by BAFF. However, IgA switching in BAFF stimulated B cells is strictly dependent on TACI [25]. The human BAFF-R gene is on chromosome 22.

Isotype switching

B cells that express and produce Ig derive from IgM^+ B cells that undergo a process of DNA rearrangement called class switch recombination (CSR). CSR changes the Ig isotype from IgM to IgG, IgE or IgA maintaining the antigen specificity. The molecular events, common for switching to all isotypes are CH germ line transcription, induction of AID (activation-induced cytidine deaminase) gene expression, deletional switch recombination and expression of mature transcripts, which are then translated at high rate by switched B cells differentiating into plasma cells [28]. The specificity of the CH switch resides at the level of CH germ line transcription.

CH germ line transcription (GLT) is mainly regulated by signals derived from cytokine-cytokine receptor interactions, such as IL-4-IL-4R, that activate γ1 and εGLT, and TGFβ-TGFβR, that activate αGLT. AID expression is mainly regulated by signals derived from specific ligand-receptor interactions such as CD40 ligand (CD40L)-CD40, in mice by lipopolysaccharide (LPS)-Toll-like Receptor (TLR) 4 and in humans by CpG rich oligo-nucleotides-TLR9 [29].

Recently BAFF and APRIL have been discovered to induce isotype switching in naive human and mouse B cells [25, 30]. We have shown that BAFF and APRIL induce isotype switching in highly purified IgM^+ B cells derived from CD40 deficient mice and depleted of any residual IgG^+, IgA^+ and IgE^+ switched B cells and plasma cells. BAFF and APRIL induced IgG and IgA switching in the absence of exogenous cytokines, but were dependent on IL-4 for isotype switching to IgE. At the molecular level BAFF and APRIL-induced isotype switching involved CH germ line transcription, AID expression and deletional switch recombination. Since the BAFF and APRIL are expressed primarily on dendritic cells, while CD40L is expressed on activated T cells, this novel pathway may underlie T cell independent isotype switching.

CVID and IgAD

CVID is characterized by recurrent bacterial infections, and is complicated by autoimmune manifestations in up to 20% of affected individuals and lymphoproliferation with splenomegaly in approximately one-third [31]. CVID is diagnosed on the basis of an impaired ability to produce specific antibodies after vaccination or exposure, markedly reduced serum levels of IgG, IgA, and frequently IgM and exclusion of other causes for antibody deficiency [32]. CVID has an estimated prevalence of 1 in 25,000 in Caucasians and is the most prevalent human primary immunodeficiency requiring medical attention. Most cases of CVID are sporadic, but at least 10% are familial, with a predominance of autosomal dominant over autosomal recessive inheritance [33]. CVID is a complex and heterogeneous disease in which defects in B cell survival, number of circulating $CD27^+$ memory B cells (including IgM^+CD27^+ B cells), B cell activation after antigen receptor cross-linking, T cell signaling, and cytokine expression have been observed [32]. The heterogeneity in the clinical symptoms and immunological defects in CVID may reflect the heterogeneity of the mechanisms leading to the deficiency.

IgAD (IgA Deficiency) is the most common form of primary immunodeficiency in the Western world. IgAD is characterized by absence, or very low level (<7 mg/dl) of serum IgA. Individuals with IgAD can be asymptomatic or be predisposed to recurrent infections, especially sinopulmonary and gastrointestinal infections. IgAD can be associated with atopy, asthma, autoimmune disorders [34, 35]. Individuals with symptomatic IgAD may

have decreased antibody response to pneumococcal polysaccharide vaccine, a carbohydrate antigen. Some individuals initially present with IgAD and then develop CVID. IgAD and CVID often coexist in members of the same family. These observations suggest that some cases of IgAD and CVID may have a common etiology.

The molecular basis of IgAD and most cases of CVID remains unknown. A small number of individuals diagnosed with CVID have X-linked agammaglobulinemia owing to mutations in BTK (Bruton's tyrosine kinase) [36]. A subset of individuals with CVID has mutations in SH2D1A, the gene mutated in X-linked lymphoproliferative disorder [37]. Some individuals with CVID express low levels of CD40L, the product of the gene mutated in X-linked hyperIgM syndrome [38]. Mutations in ICOS have been identified in 9 individuals with CVID [39]. Family studies showed that inheritance vary from an autosomal dominant to an autosomal recessive transmission. Genetic linkage analysis of IgAD and CVID families identified the presence of susceptibility loci in chromosome 6 within MHC (Major Histocompatibility Complex) locus near the regions of class I, II, and III [33]. The DR/DQ locus has been reported to be the strongest predisposing locus. MHC class II genes play a fundamental role in antigen presentation to T helper cells that in turn provide help to B cells for a proficient Ig (immunoglobulin) production. Therefore, particular MHC class II alleles may contribute to the Ig deficiency and to the associated autoimmune manifestations. Other IgAD susceptibility loci located in different chromosomes have been described although with lower linkage score [40]. These studies suggest that IgAD and CVID might represent a range in the penetrance of the same disease.

Failure to produce IgA in IgAD patients and Igs in CVID patients is understood to be due to the failure of B cells to differentiate into sufficient number of plasma cells. Studies on the molecular events leading to IgA production [41, 42] revealed that some IgA deficient patients have impaired switching to IgA while others present a post-switch defect [42–44]. Impaired somatic hypermutation was described in 25% of CVID patients in one study [45, 46] and in 77% of the patients in another [47]. There is also evidence for a global isotype switching defect in some individuals with CVID [31–33].

Mutations in TACI result in CVID and IgAD

We and others have recently found that *TNFRSF13B* gene which encodes TACI is mutated in a subgroup of patients with CVID [48, 49]. In addition we identified TACI mutations in a family with IgAD. Our group found four different mutations in TACI in 5 of 20 individuals with CVID and 1 of 16 individuals with IgAD. None of these mutations was present in 50 healthy controls [48]. All six patients were index cases with other family members found bearing the same mutation. Grimbacher's group found five mutations in TACI in 13 of 162 individuals with CVID [49]. In three of the patients' families other members bearing the same mutation were identified. In total six mutations in the TACI gene have been identified to date. The location of the mutations in TACI is illustrated in Fig. 3.

The mutations are distributed in all regions of the TACI molecule, three in the extracellular domains, one in the transmembrane domain, and two in the intracellular domains. Three of these mutations are missense mutations, involving a change in one codon that causes a replacement of one amino acid by another in the protein sequence: cysteine (C)104 to arginine (R), alanine (A)181 to glutamic acid (E), and R202 to histidine (H). Two are nonsense mutations, involving a change in one codon that results in a stop codon: serine (S)144 to stop codon (X) and S194X. One is an insertion of one base, adenine, at the 204th (A204) nucleotide

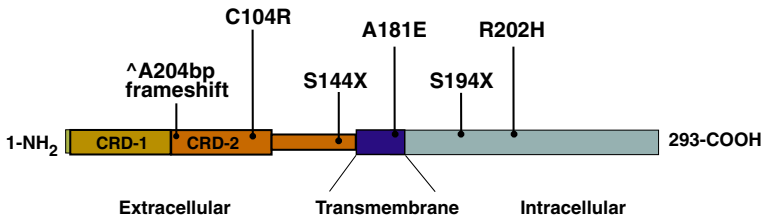

Fig. 3 TACI mutations in CVID

from ATG. This mutation results in a frameshift following aa 68, or 23 in the TACI isoform missing the CRD1, and premature termination of the protein 11 aa downstream.

Naïve B cells from CVID patients with TACI mutations were severely impaired in their ability to secrete IgG and IgA in response to APRIL in vitro [48]. Although, IgG and IgA secretion by normal naïve B cells in this system is likely to represent isotype switching, it is also possible that it may reflect increased survival of already switched contaminating B cells, or increased Ig secretion by these cells in response to APRIL stimulation. Since, we have previously shown that TACI, but not BCMA, is responsible for IgG and IgA isotype switching and secretion in response to APRIL [25], these results suggest that TACI-mediated signaling was impaired in the patients B cells.

Mechanisms of B cell deficiency in patients with TACI mutations

C104 is located in the second CRD of TACI and forms disulfide bonds with the C93 stabilizing the second h2 loop of CRD2 [16]. The C104R mutation was demonstrated to abolish binding of APRIL and BAFF to TACI [48, 49]. In the majority of CVID cases with the C104R mutation and in the only case of IgAD with this mutation, only one allele is affected. This raises the question of why patients heterozygous for this mutation fail to respond to APRIL and BAFF. The answer may lie in the potential capacity of TNFR family members to undergo ligand independent preassociation [50, 51] and with the fact that efficient binding of the trimeric ligand may require simultaneous binding to three receptor surfaces. Preassociation of WT (wild type)-C104R mutated TACI may result in interference with ligand binding and subsequently ligand-induced signaling. A similar mechanism may explain the B cell deficiency in patients heterozygous for the A204 insertion because the putative truncated protein may interact with WT protein and interfere with pre-assembly of TACI molecules. However the putative truncated protein may not exist because of RNA or protein degradation. If this is the case the explanation is that the expression of a single WT normal allele of TACI is not sufficient for effective signaling. On the other hand mice heterozygous for a null TACI allele have having normal B cell function [13]. However, the phenotype of the $TACI^{+/-}$ mice may not reflect the phenotype of patients carrying a heterozygous TACI mutation.

The S144X leads to premature termination of the protein synthesis. The putative product would not be membrane anchored. The S144X mutation described is homozygous. No TACI protein or mRNA was detected in these patients, suggesting that this mutation confers a susceptibility to RNA or protein degradation. B cells from one such patient were shown not to bind TACI [49].

A181 is located in the transmembrane domain in proximity of the intracellular portion of TACI. We showed that A181E mutant is expressed and binds BAFF normally [48]. A181E results in the substitution of a neutral aa with a negatively charged acidic aa. This may interfere with the capacity of the receptor to aggregate upon ligand cross-linking. Alternatively, the mutated protein may be more accessible to proteolytic cleavage or undergo a conformational change that may affect its capacity to signal, e.g., by interfering with its ability to interact with CAML and induce NF-AT activation, because the CAML binding site is proximal to the transmembrane domain. Since this mutant is expressed and binds ligand it may act as a dominant negative by assembling with WT TACI and disrupting signaling.

R202 is in the region involved in CAML binding. The R202H mutant is expressed on transfectants and binds the ligand [48]. Preliminary data suggests that the R202H mutation may affect the TACI-CAML interaction and thus block TACI-induced NF-AT activation (our unpublished observation). Therefore, it may assemble with WT TACI and disrupt signaling by disrupting CAML binding.

The S194X mutation was present in a two related CVID patients homozygous for the mutation. S194X mutation generates a truncated form of TACI in which the region of intracellular domain that contains the docking sequences for TRAF 2, 3 and 6 is deleted. Since these TRAF proteins are important for CD40 isotype switching, the S194X mutant would be impaired in its ability to induce isotype switching.

Penetrance of TACI mutations

There was a perfect correlation between the presence of the mutated allele and the occurrence of CVID or IgAD in family members of the four patients we studied (Fig. 4). In these four families twelve individuals who carried the mutant allele had CVID or IgAD. About 11 of these 12 gave a history of recurrent infections, and four were on IVIG replacement therapy. In contrast, all six individuals who had normal *TACI* genes had normal levels of IgG and IgA and were free of recurrent infections. There was a wide heterogeneity in the severity of the clinical symptoms in the family members with TACI mutations. Symptoms ranged from severe to mild or even non-existent. There was also a wide variability in serum IgG and IgA levels. In the same family TACI mutation could be associated with CVID or IgAD (Fig. 4).

In Grimbacher report the two brothers with the same homozygous S144X mutation presented very different phenotype [49]. This suggests that TACI mutation has different penetrance, i.e., the frequency with which a specific phenotype is expressed by individuals with a specific genotype. This may be due to both genetic and environmental modifiers. In this respect, mutations in the TNF gene are known to correlate with the severity of CVID [52]. Furthermore, the MHC locus shows linkage to CVID and IgAD. Thus at least TNF and MHC alleles may influence the penetrance of TACI mutations.

Conclusion and therapeutic implications

In summary, TACI mutations leading to an immunodeficiency account for about 5% of the cases of CVID, the highest incidence of a monogenic defect ever found in CVID. Moreover, the genetic transmission in most of the CVID patients with TACI mutation is autosomal dominant with variable penetrance in family members carrying the mutated

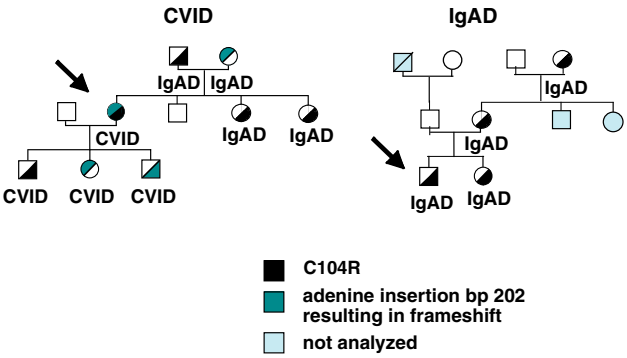

Fig. 4 Family trees of an index patient with CVID and an index patient with IgAD, both indicated with an arrow

allele. These findings should allow accurate genetic diagnosis in a subgroup of patients with CVID and their relatives. It will remain to be seen whether useful genotype-phenotype correlations can be drawn in patients with TACI mutations regarding severity of infections, development of granulomas, autoimmunity and malignancy.

TACI normally delivers an apoptotic signal to B cells as evidenced by in vitro studies and by the development of autoimmunity and B cell lymphoproliferation in TACI deficient mice. Defective TACI signaling in patients with CVID may underlie the susceptibility of these patients to develop autoantibodies, benign lymphoproliferation with splenomegaly and malignant lymphoma and non-lymphoid malignancies. Finally, the fact that TACI is predominantly expressed in B cells suggests that autoimmunity and B cell malignancy may develop in a B cell autonomous fashion in patients with TACI mutations. This raises the possibility that anti-CD20 monoclonal antibody may be of value in patients with TACI mutations who develop life threatening autoimmune disease or B cell lymphoma.

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