Common Variable Immunodeficiency

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ABSTRACT: Common variable immunodeficiency is the most prevalent clinically significant antibody deficiency at all ages. The disorder is defined principally by characteristic infection susceptibility with hypogammaglobulinemia and impaired-specific antibody response. Several recent large registry-based studies have defined distinct phenotypic subtypes. Several studies have also correlated specific immunologic markers with these phenotypes. The biochemical or genetic abnormality in the majority of patients remains unknown. Recently, several molecular genetic lesions have been defined. Among these, mutations of inducible costimulator, and CD19, appear to be disease causing by themselves. These account for about 1% of cases. Other mutations or polymorphisms, such as in the human homolog of *Escherichia coli* MutS 5 (MSH5), and transmembrane activator and calcium mobilizing ligand interactor, seem to be disease associated in 5–10% of patients, but may require additional immunologic abnormalities for full expression of the phenotype, as unaffected heterozygotes have also been described. (*Pediatr Res* **65:** 13R–19R, 2009)

Clinical Features of CVID

Common variable immunodeficiency (CVID) is a form of predominantly humoral primary immunodeficiency. Symptoms may begin at any time of life, including the extremes of both young and old age (1–3). Major characteristics include recurrent infections, principally bacterial and viral of the respiratory tract. In one recent French registry study (DEFI Study) of 252 patients, 95% had one or more of the following: bronchitis, sinusitis, and pneumonia. Not surprisingly, common bacterial pathogens such as *Streptococcus pneumoniae* and *Hemophilus influenzae* were most often isolated. Granulomatous or lymphocytic interstitial lung disease occurs in a subset of patients and may be associated with human herpesvirus 8 (4). Granulomas may also involve other organs and resemble sarcoid. Furthermore, in the DEFI study, 47% of patients had diarrhea (intermittent or chronic); *Giardia, Salmonella,* and *Campylobacter* were common isolates (2). Enteroviral intestinal infections may disseminate and cause meningoencephalitis.

Autoimmune disease is common in CVID (5). One recent survey reviewed seven published studies comprising 831 patients altogether (6). The reported prevalences of autoimmune disease ranged from 17 to 50%, and it was present in 27% of the overall patient population. Immune thrombocytopenic purpura and autoimmune hemolytic anemia were by far the most common diagnoses, followed by aseptic nonerosive seronegative inflammatory arthritis. Additional disorders observed include inflammatory bowel disease, vasculitides (some resembling systemic lupus erythematosus), and others.[1]

Approximately 10% of patients with CVID have a lymphoproliferative disorder (7). This manifests most frequently as splenomegaly, lymphadenopathy and interstitial lung disease, as described above. The relative risk of lymphoma in patients with CVID compared with the general population is in the range of 10- to 20-fold higher (7). Most of these are B-cell non-Hodgkin lymphoma, although Hodgkin lymphoma is sometimes seen. EBV is found very infrequently (8). A European registry of CVID has collected 334 patients with a cumulative 9461 patient-years of observation (1). These authors distinguish five principle CVID clinical phenotypes: no complications (recurrent infections only), and one or more of the following with or without recurrent infections: autoimmunity, polyclonal lymphocytic infiltration, enteropathy, and lymphoid malignancy. Eighty-three percent of the entire cohort had one of these five phenotypes only, whereas the remainder had two or more complications with or without infections. Survival in the group with infections alone (48% of all patients) was significantly prolonged in comparison with those with one or more complications.

Immunologic Features of CVID

By definition, all patients have low serum IgG, often with low IgA and or IgM, and some clear impairment of specific antibody response to infection or vaccine challenge (9). Not surprisingly, with such a relatively nonspecific clinical and laboratory definition (overall), additional immunologic laboratory findings are heterogeneous. In comparison with healthy individuals, B-cell number and *in vitro* function may be normal or low. CD4 and or CD8 T-cell numbers may also be normal or low. A variety of additional immunologic findings have been reported in relatively small series of patients. The significance of many of these functional abnormalities is unclear, given the underlying heterogeneity of the overall population of patients. Several are listed in Table 1 (10–29).

Abbreviations: APRIL, a proliferation-inducing ligand; **BAFF,** B-cell activating factor; **CVID,** common variable immunodeficiency; **ICOS,** inducible co-stimulator; **MSH5,** *E. coli* MutS homolog 5; **TACI,** transmembrane activator and calcium-mobilizing ligand interactor

Table 1. *Immunologic abnormalities in patients with CVID in comparison to healthy controls*

Finding	References
T cells	
Impaired thymic development and reduced thymic output	(10, 11)
Altered cytokine production (various)	(10, 12)
Altered surface marker expression	(10, 13–15)
Altered signal transduction (decreased expression of vav)	(16)
Impaired signaling *via* TNF-RII (TNFRSF1B)	(17)
Increased spontaneous apoptosis (T-cell turnover)	(10)
Reduced regulatory T cells	(18)
Reduced naïve CD4 and CD8 T cells	(10)
Restricted T cell receptor beta V gene repertoire	(10)
Differential gene expression	(10)
B cells	
Altered surface marker expression	(13, 14, 19)
Altered development of plasma cells	(20)
Monocytes	
Altered cytokine production	(12)
Dendritic cells	
Impaired maturation (reduced numbers)	(21, 22)
Altered distribution	(23)
Altered cytokine production	(24, 25)
Innate immunity	
Impaired signaling via toll-like receptor 9	(26)
Metabolic abnormalities	
Vitamin A deficiency	(27)
Hypoleptinemia	(28)
Insulin resistance	(29)

Many reports have focused on identifying more refined immunologic markers to distinguish subsets of patients within CVID or to predict clinical course. We will further describe some potentially useful classification schemes based on immunologic markers that have emerged recently.

Circulating naïve B cells have surface IgM and IgD. After antigen and T-cell stimulation in germinal centers, they may undergo class switching whereby they lose surface IgM and IgD and may express IgG, IgA, or IgE. Memory B cells express the surface marker CD27 (tumor necrosis factor receptor superfamily member 7 or TNFRSF7). Thus, naïve B cells are $IgM^+IgD^+CD27^-$; "unswitched" memory B cells are $IgM^+IgD^+CD27^+$; and "switched" memory B cells are $IgM^-IgD^-CD27^+$. Memory B cell populations form the basis of a few classification schemes for patients with CVID (Table 2) (30–35). Several additional studies also suggest that reduced percentage of switched memory B cells correlates better with infections and autoimmunity than do serum immunoglobulin and specific antibody responses (36,37). In one such study, females were found to have significantly higher numbers of switched memory B cells in comparison with males (38). The significance of this finding is unknown. At least one study suggests that reduction in unswitched memory B cell numbers also correlates well with clinical complications such as pneumonia (39), although others have not found this association (38).

A large European multicenter trial has recently revisited the matter of CVID classification based on B-cell phenotypes (the EUROclass trial) (40). This study included 303 patients and defined four main groups: those with <1% B cells, those whose switched memory B cells were <2% of all B cells, and patients with expansion (>9% of all B cells) of transitional ($CD38^{hi}IgM^{hi}$) B cells or expansion of $CD21^{low}$ B cells (>10% of all B cells). The most robust statistical associations with phenotypes were a) low switched memory B cells with granuloma; b) expanded transitional B cells and lymphadenopathy; c) expanded $CD21^{low}$ B cells and splenomegaly.

Low naïve CD4 T cells correlate well with overall clinical severity and splenomegaly (10). In this study, low serum IgA was the only other major correlate with clinical severity. Low naïve CD4 cells also correlate significantly with the Warnatz classification based on memory B cell phenotypes (Table 2). Low naïve CD4 cells are predominantly in Warnatz groups Ia and Ib (10). However, the concordance between these classification schemes is only approximately 60%. Other abnormalities of T-cell function that predominated in the patients with the lowest naïve CD4 cell numbers included a high degree of T-cell activation exhibited by expression of CD95 (Fas) and HLA-DR, the highest rates of proliferation and apoptosis, and the greatest restriction in T-cell receptor V beta gene repertoire. In patients in the lowest tertile of naïve CD4 cell number, these authors found significantly increased expression of mRNA for CD9 and CREB1 (cAMP response element binding, 11-fold and 5-fold, respectively), and reduced expression of HCFC1 (host cell factor C1, 14-fold).

Both myeloid and plasmacytoid dendritic cell populations are reduced in CVID (21). The number of dendritic cells correlates with total number of B cells and percentage of switched memory cells. As has been seen in other studies, they also correlate with clinical features such as infections, granulomatous disease, autoimmunity, splenomegaly, etc. In the European registry study, only limited immunologic correlations with phenotypes were sought (1). Increased IgM was associated with lymphocytic infiltration and malignancy; increased CD8 cells were inversely related to the risk for autoimmune disease.

Diagnosis

Given the nonspecific nature of the clinical presentation and fundamental laboratory definition of CVID, the diagnosis remains predominantly one of exclusion. In the adult group in

Table 2. *Classifications of CVID based on memory B cell phenotype*

Classification scheme	Group	Memory B cells	Splenomegaly or LPD*	Granulo mas	Auto immunity	Serum immunoglobulin	Specific antibody
Piqueras *et al.* (34)	MB0	All CD27$^+$ low	+	+	+		
	MB1	Low IgM/D$^-$CD27$^+$	+	+	+	Very low	Very low
	MB2	Normal			+	Low	Low
Warnatz *et al.* (35)	Ia	Low IgM/D$^-$CD27$^+$ and low CD21	+	+	+	Very low	Very low
	Ib	Low IgM/D$^-$CD27$^+$ and normal CD21		+	+	Very low	Very low
	II	Normal			+	Low	Low

LPD, lymphoproliferative disease.

particular, secondary immunodeficiencies must be excluded. Although nonspecific, the main diagnostic criteria are, at least, straightforward. Thus, it may be surprising that many patients are ill for many years before the diagnosis is made. It seems most likely this is due to lack of recognition on the part of clinicians.

In the European registry study, the mean and median ages at onset of symptoms were 26.3 and 24 y, respectively (1). At diagnosis, these ages were 35.3 and 33 y, respectively. The mean and median years of delay between symptom onset and diagnosis were 7.5 and 5, respectively (range 0–61 y). Twenty percent of patients were diagnosed more than 15 y of the onset of symptoms, and there was an inverse correlation between the age of onset and the delay in diagnosis. In the DEFI study, the median age at onset of symptoms was 19 y, and median age at diagnosis was 33.9 y (2). The delay in diagnosis was greatest for patients identified before 1990, in comparison with those diagnosed after 1990, suggesting increased awareness and screening for hypogammaglobulinemia in adults presenting with recurrent infections. Nevertheless, the median delay in diagnosis after the onset of symptoms was still 2.9 y even in the group diagnosed after 1990. In an Italian study of 224 patients with CVID, the mean age at onset was 16.9 y and mean age at diagnosis was 26.6 y (mean delay 8.9 y) (3).

It may be said that individuals are "misdiagnosed" with CVID, if they are ultimately found to have a molecular defect associated with a previously defined and distinct primary immunodeficiency syndrome. This has occurred in patients with mutations of Bruton's tyrosine kinase (*BTK*, associated with X-linked agammaglobulinemia) (41,42), SLAM-associated protein or SAP (encoded by *SH2D1A* and associated with X-linked lymphoproliferative syndrome) (43). On the other hand, mutations or polymorphisms in several genes not previously associated with primary immunodeficiency have been described in the CVID population, and these patients are said to have CVID (possibly) due to, or associated with, mutations of these genes. They include inducible T-cell costimulator (*ICOS*), *CD19*, the human homolog of *Escherichia coli* MutS 5 (*MSH5*), and transmembrane activator and calcium mobilizing ligand interactor (TACI), also called tumor necrosis factor receptor superfamily member 13B (*TNFRSF13B*).

ICOS Deficiency

A total of nine individuals worldwide have been found to have mutations of *ICOS* (44). All of these individuals have the same founder mutation (deletion of a large segment of the gene) arising originally in the Black Forest region of Germany. These patients have recurrent infections without the autoimmune, lymphoproliferative or malignant complications often seen in CVID. All but one had adult onset of symptoms. These patients have panhypogammaglobulinemia, poor vaccine responses, and low B cells, including the memory subset. Thus, they represent a discordance from the association of low memory B cells and noninfectious complications of CVID observed in the larger population.

ICOS is a member of the CD28 family and interacts with a member of the B7 group of molecules known as ICOS ligand. ICOS is induced on T cells after activation, whereas ICOS ligand is expressed constitutively on antigen-presenting cells and B cells. This signaling pathway leads to increased production of IL-10, important for terminal B-cell development into memory B cells and plasma cells. ICOS is also important for activation of helper T cells and cognate T cell help for antibody production (45). ICOS-L knockout mice have the same phenotype as ICOS knockouts (46). To date, ICOS-L mutations have not been identified in patients with CVID.

CD19 Deficiency

Five patients with recurrent infections, hypogammaglobulinemia, poor vaccine responses, and low memory B cells have been found to have mutations in CD19 (47,48). All patients had onset of symptoms in the first decade of life, and developed thrombocytopenia. CD19 is a component of a B-cell signaling complex. It is expressed in association with CD21 (also called complement receptor 2, or CR2), CD81 (TAPA-1) and CD225 (Leu-13, or interferon-induced transmembrane protein 1). The physiologic ligand of CD21 is the C3 component of complement fragment C3dg; it is also the EBV receptor. CD19 signals *via* the Lyn tyrosine kinase and the CD19 complex reduces the threshold for B-cell activation *via* the immunoglobulin receptor.

Polymorphisms of MSH5

Selective IgA deficiency is a distinct diagnostic entity that shares some clinical features with CVID (49). Some patients

with IgA deficiency may progress over time to CVID. CVID and IgA deficiency have been associated with HLA haplotypes A1-B8-DR3, B14-DR1, and B44-DR7 (50,51). As many as 13% of patients homozygous for A1-B8-DR3 may be IgA deficient. The peripheral blood B cell number is statistically somewhat higher in patients with either of these HLA-B alleles (independent of DR) in comparison with those with other HLA-B types (50).

MSH5 has roles in meiosis, DNA mismatch repair, and immunoglobulin class switching (51). Recently, polymorphisms in *MSH5* have been found in some patients with CVID and selective IgA deficiency. The *MSH5* gene is in the class III MHC locus, and these polymorphisms are associated with the A1-B8-DR3 extended haplotype. Although these polymorphisms occur with greater frequency in affected patients, they are also found in healthy individuals, and functional consequences have not yet been demonstrated. Additional disease determinants in these patients have not yet been identified.

TACI Deficiency

Between 5 and 10% of patients with CVID are either homozygous or heterozygous for mutations of TACI, whose official designation is tumor necrosis factor receptor superfamily member 13B, or TNFRSF13B (52–55). The A181E and C104R mutations in the transmembrane and extracellular regions of TACI, respectively, have been particularly associated with disease in heterozygotes (and homozygotes). However, the pathogenetic role of these (and other) mutations still requires clarification. Some heterozygotes may be asymptomatic (56,57).

TACI is an element of a complex intercellular signaling system involving a subset of the tumor necrosis factor/tumor necrosis factor receptor (TNF/TNFR) superfamilies. These interactions are summarized in Figure 1. TACI is expressed on B cells after activation by a variety of stimuli such as ligation of toll-like receptor 9, ligation of IgM, and signaling *via* CD40, also interleukins-2 and -10; expression persists on memory B cells and plasma cells (58,59). TACI expression is prominent in marginal zone B cells and a subset of CD27$^+$ B cells (59,60). TACI may also be found on activated T cells, monocytes, and dendritic cells (61).

TACI ligands BAFF (B-cell activating factor, TNFSF13B) and a proliferation-inducing ligand (APRIL, TNFSF13) are expressed on macrophages and dendritic cells (58). BAFF is also expressed on neutrophils and APRIL is also expressed on some activated T cells. The multimeric (60-mer) form of BAFF exclusively signals *via* TACI, whereas BAFF-R (expressed exclusively on B cells) also can signal after ligation by soluble BAFF 3-mer (Fig. 1) (62). TACI also interacts with the proteoglycan syndecan-2 (63). Signaling between TACI and its ligands influences B cell activation, survival, class switching, and memory B cell formation.

Note that CD40 is also a member of the TNFR superfamily (it is TNFRSF5) and CD40 ligand (CD0L, also called CD154) is TNFSF5. CD40 is expressed on B cells and mononuclear cells including dendritic cells, and endothelial cells, whereas CD40L is expressed on activated T cells. CD40-CD40L interactions are entirely distinct from those in the TACI system, and there is no cross-interaction. In mucosal tissues B cells are in proximity to dendritic and epithelial cells that may express BAFF and APRIL in response to signals generated *via* toll-like receptors (64). This permits rapid T cell independent immunoglobulin production. In contrast, in secondary lymphoid tissues such as spleen or lymph nodes, B cells are in proximity to T cells and receive signals *via* CD40L leading to germinal center formation and T-dependent immunoglobulin production (65). TACI can mediate class switching to IgA, though to a lesser degree than CD40 (66). Signals delivered through TACI also amplify plasma cell differentiation and immunoglobulin production after CD40 or toll-like receptor signaling (67).

TACI-deficient mice have low serum IgA and impaired antibody response to thymus-independent type 2 antigens (normally generated in the absence of cognate T cell help for B cells) (68). Although TACI has important roles as a coactivator with various signals, it also regulates B-cell expansion. TACI-deficient mice have increased numbers of circulating B cells and splenomegaly and are prone to autoimmunity and lymphoma (68,69).

The intracellular domain of TACI associates with various TNF receptor associated factors 2 and 3 (TRAFs 2 and 3) and calcium-mobilizing ligand (CAML) (58). Downstream intermediates link TACI to pathways through the nuclear factor kappa B (NF-κB), and the transcription factors nuclear factor of activated T cells (NF-AT), and activator protein-1 (AP-1). The mechanistic links between CD40, TACI, and BAFF-R to class switching are not yet clear. Association with TRAF2 and TRAF3 is necessary, but not sufficient because many other TNFRs signal through these intermediates and do not promote class switching. Another pathway associated with TACI involves CAML, which enables calcium mobilization during cellular activation. Additional signaling pathways linked to CD40 mediating class switching have not yet been described.

TACI forms multimeric complexes before ligand binding (70). The human C104R mutant (and the murine C76R ho-
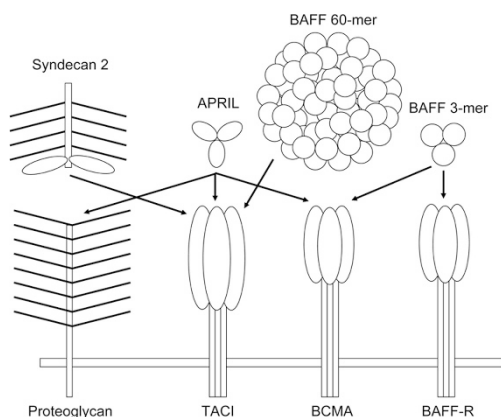

Figure 1. Signaling interactions among TACI, related receptors, and their ligands. BCMA is B-cell maturation factor, also tumor necrosis factor receptor superfamily member 17 (TNFRSF17). See text for other abbreviations and details.

molog) does not bind ligand (BAFF) but can form multimers with wild-type TACI. Although the mutant TACI molecules do not inhibit ligand binding by the wild-type TACI, downstream NFkB signaling is blocked by this association.

Patients with CVID with TACI mutations may exhibit the full spectrum of clinical complications including recurrent infections, autoimmune disease, lymphoproliferation, and lymphoma, low IgG with or without low IgA, poor responses to vaccines (particularly pneumococcal polysaccharides), low B-cell number and low switched memory B cells. One study of 176 patients with CVID identified 13 (7.6%) heterozygous for various TACI mutations (57). The rates of autoimmune thrombocytopenia and splenomegaly were significantly increased in this group, in comparison with patients with CVID without TACI mutations. Defective responses to stimulation with APRIL *in vivo* were noted in some TACI-mutant patients, but this was also observed in patients without TACI mutations. Altogether, eight healthy first-degree relatives were heterozygous for the same mutations and had normal responses to APRIL. Additional disease-defining genetic or environmental determinants have not been described in these individuals to explain the variable penetrance of TACI mutation. In a separate study, the serum of 77 patients with CVID was found to have significantly elevated levels of TACI, BAFF, and APRIL in comparison with a group of 21 controls (71). However, within the patients, the levels did not correlate with clinical, immunologic laboratory or genetic (TACI mutation) phenotypes.

There may be different functional consequences of distinct TACI mutations and some may act in a dominant negative manner and others may impair signaling by haploinsufficiency. However, deleterious TACI mutations alone cannot be said to be disease causing because they are found in 1% of the general population including apparently healthy first-degree relatives of patients with CVID (see above). No candidate genes modifying expression of TACI mutation have yet been described.

Newborn mice express very little TACI and do not respond to BAFF and APRIL (72) The same is true of preterm and newborn humans (73). This may underlie or contribute to the relatively low responsiveness to polysaccharide antigens (for example, pneumococcal capsule) in newborns. The defect can be abrogated by coupling CpG oligodeoxynucleotides (TLR9 agonists) to polysaccharide immunogens (72).

The adenovirus E3–6.7 K protein may be a viral homolog of TACI (74). The E3–6.7 K protein binds to and colocalizes with CAML in an endoplasmic reticulum compartment and can inhibit calcium flux and apoptosis. This could be a mechanism for enhancing survival of infected cells.

Atacicept is a TACI-immunoglobulin fusion protein that has been developed for potential therapy of autoimmune disease (trials have included systemic lupus erythematosus and rheumatoid arthritis) and B cell lymphomas (75–78). The rationale for autoimmune disease is to inhibit signaling *via* BAFF and APRIL and hopefully to diminish ongoing autoimmune B cell activation. In the setting of B cell malignancy, BAFF and APRIL are often overexpressed and could provide a survival or proliferation signal mediated by TACI. Treated patients have exhibited declines in serum IgG and B cell numbers. The drug is well tolerated, but its efficacy in any of these diseases is not yet established.

Conclusion

Despite the descriptions of molecular defects in subsets of patients with CVID, more than 90% of cases are due to mechanisms that have not yet been described. As our understanding grows regarding signaling *via* TACI, related receptors, and BAFF and APRIL, the final common pathway may soon come to light. Even if the final answers lie elsewhere, this is yet another example where study of primary immunodeficiency yields fundamental breakthroughs that may have far-reaching consequences for understanding of and intervention in other diseases.

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