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Review Article

Genetic defects and the role of helper T-cells in the pathogenesis of common variable immunodeficiency

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Abstract

Common variable immunodeficfiiency (CVID) is a primary immunodeficiency syndrome representing a heterogeneous set of disorders resulting mostly in antibody deficiency and recurrent infections. However, inflammatory and autoimmune disorders and some kinds of malignancies are frequently reported as a part of the syndrome. Although it is one of the most widespread primary immunodeficiency, only recently some genetic defects in CVID have been identified. Mutations have been detected in inducible T-cell costimulator (ICOS), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), B-cell activating factor-receptor (BAFF-R), B-cell receptor complex (CD19, CD21 and CD81) and CD20. On the other hand, recent studies have shown a decrease in T-helper-17 cells frequency and their characteristic cytokines in CVID patients and this emphasis on the vital role of the T-cells in immunopathogenesis of the CVID. Furthermore, in the context of autoimmune diseases accompanying CVID, interleukin 9 has recently attracted a plenty of considerations. However, the list of defects is expanding as exact immunologic pathways and genetic disorders in CVID are not yet defined. In this review, we have a special focus on the immunopathogenesis of CVID, recent advances in understanding the underlying etiology and genetics for patients.

Key Words: B-cell activating factor receptor, common variable immunodeficiency, inducible T-cell co-stimulator, interleukin 9, T-helper-17, transmembrane activator and calcium modulator and cyclophilin ligand interactor

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INTRODUCTION

As a primary immunodeficiency, common variable immunodeficiency (CVID) is characterized by low levels of serum immunoglobulins (Ig) and recurring bacterial infections. Males and females are affecting equally. Although there are no clear-cut data on the prevalence of CVID, prevalence ranging from 1:10,000 to 1:50,000 or 1:100,000, is estimated and it is believed to be the most prevalent human primary immunodeficiency diseases (PID) requiring medical consideration.[1-3] The onset of CVID is at greater than 2 years of age.[4] CVID patients have diverse clinical presentations and manifest different types of immunodeficiencies.[5,6] A marked decrease of IgG and of at least one of the IgM or IgA isotypes can be used to diagnosis of CVID, while the absence of isohemagglutinins and/or failure to response to specific antigens and other defined causes of hypogammaglobulinemia are excluded.[7] Clinically,

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Patients have an increased susceptibility to infections with signs of autoimmunity and an increased risk of malignancy.[8]

As about 90% of CVID patients have normal numbers of peripheral B lymphocytes, presumably the defects are due to the later stages of B-cell development.[9] However, apart from low Ig production by B-cells in CVID patients, other immunological abnormalities such as T-cell dysfunction and monocyte/macrophage hyperactivity are reported in a large proportion of patients.[10] Approximately, half of the cases have signs of T-cell deficiencies contributing to the defective antibody production.[11,12] It's demonstrated that CVID patients have decreased numbers of T-helper-17 (Th17) cells in their circulation.[13] Mutations have been identified in various B-cell related inducible T-cell costimulator (ICOS), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), B-cell activating factor-receptor (BAFF-R), in members of the CD19-B-cell receptor (BCR) complex (CD19, CD21 and CD81) and CD20 (Table1). Moreover, polymorphisms in genes involved in deoxyribonucleic acid (DNA) repair (MSH5, MSH2, MLH1, RAD50 and NBS1) have also been reported in patients with CVID.[4,14-20] Among the CVID patients, only 10-20% of cases have a positive family history while most cases arise sporadically.[7] In the most families, CVID is inherited in an autosomal dominant pattern, but autosomal recessive inheritance is also seen in a significant minority.[21]

GENETIC DEFECTS PREDISPOSING FOR CVID

ICOS deficiency

ICOS is a member of Ig-like co-stimulatory surface molecules, which expresses only on activated T lymphocytes. In human, this is encoded by the ICOS gene on chromosome 2q23.[21,22] The ligation of ICOS with its ligand on B-cells stimulates the differentiation of T lymphocytes into T follicular helper (TFH) cells. The latter cells are essential for the creation of the germinal center (GC) in lymphoid follicules.[23] Accordingly, recent researches demonstrate that the formation of GCs is impaired in ICOS-deficient patients.[21] In lymph nodes of an ICOS-deficient patient, disturbed GC formation has demonstrated by follicles analysis.[24] Bossaller *et al*. have reported that ICOS-deficient patients had a severe decrease in $CXCR5^+$ positive/$CD4^+$ T-cells and almost complete absence of $CD57^+/CXCR5^+/CD4^+$ T-cells.[24]

This defect in GC formation may be due to the low production of interleukin (IL)-10 by ICOS-deficient $CD4^+$ T lymphocytes, which result in severe decrease in the number of $CD27^+$ memory B-cells and plasma cells. ICOS also plays an essential role in clonal expansion of effector Th2 cells.[25,26] ICOS also regulates Th2 cell differentiation by enhancing NFATc1 expression and initial IL-4 production during early T-cell activation by antigens.[27]

Reported by Grimbacher *et al*. in 2003, the first genetic defect detected in patients with CVID was ICOS deficiency (*CVID1,* Mendelian inheritance in man (*MIM*)#607594) (Table 1) as an autosomal recessive disorder.[28,29] However, based on a research in the Black Forest region of Germany, only 9 out of 226 patients with CVID have been found to have ICOS mutations.[29] Altogether, 11 individuals from 5 different families have been identified so far, 9 of them had the same mutation in ICOS.[28-30] A homozygous deletion of a region spanning from intron 1 to intron 3 of the ICOS gene (1815 bp) was found in the first nine individuals (from four families) identified.[28,29]

Table 1: Types of CVID basis on deficient gene

Type	Deficient gene	Chromosome location	Number of related mutations identified so far
CVID 1	ICOS	2q33.2	2
CVID 2	TACI *(TNFRSF13b)*	17p11.2	16
CVID 3	CD19	16p11.2	2
CVID 4	BAFFR *(TNFRSF13c)*	22q13.2	2
CVID 5	CD20 (MS4A)	11q12.2	1
CVID 6	CD81 (TAPA-1)	11p15.5	1
CVID 7	CD21 *(CR2)*	1q32	2

CVID: Common variable immune deficiency, ICOS: Inducible T-cell costimulator, MS4A: Membrane-spanning 4A, TAPA-1: Target of the antiproliferative antibody 1, CR2: Complement receptor 2, TNFRSF: Tumor necrosis factor receptor superfamily

TACI deficiency

TACI is belonging to the tumor necrosis factor (TNF) receptor superfamily and is expressed both on activated T lymphocytes and B lymphocytes.[31,32] TACI molecules are encoded by the *TNFRSF13B* gene located at the short arm of human chromosome 17 (17p11.2).[32] BAFF and a proliferation-inducing ligand (APRIL) are the known ligands for TACI.[33] Ligation of TACI induces class-switch recombination events in B-cells.[34-37] In 2005, mutations in *TNFRSF13B* have been described in CVID patients.[16,38] A variety of mutations in TACI *(CVID2, MIM#240500)*(Tabel1) have identified in cohorts of patients with CVID by multiple studies.[16,38-40] However, the earliest studies showed that the TACI mutations more frequently are founded in C104R and A181E positions.[41] All together, the incidence of TACI deficiency patients is estimated to be around 5-10% of CVID patients.[42]

Based on clinical findings, TACI mutations show a range of clinical symptoms from no infection to

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very severe infections, autoimmune manifestations, lymphoma and other cancers. This suggests that other genetic and environmental factors may contribute to this variable disease spectrum.[32,43] Recent studies demonstrate that TACI deficiency patients may be more prone to lymphoproliferation and autoimmunity as in a cohort of 564 patients, TACI mutations were shown to be strongly associated with autoimmunity (most commonly autoimmune thrombocytopenia) and lymphoproliferation (splenomegaly, lymphadenopathy, nodular lymphatic hyperplasia).[4]

CD19 deficiency

In human, CD19 protein is encoded by the *CD19* gene and it is located on the short arm of chromosome 16 (16p11.2).[18] CD19 is a member of BCR co-receptor complex together with CD21, CD81 target of the antiproliferative antibody 1 (TAPA-1) and CD225 on mature B-cells.[44,45] Unlike CD81 and CD225, CD19 and CD21 are B-cell specific antigens.[46] Recognition of antigen attached to C3d by the BCR and CD21 respectively results in dual signaling through the BCR and the CD19 complex. In this manner, this complex acts as a link between the innate and adaptive immune systems.[23] $CD19^{-/-}$ B-cells show a decrease in serum Ig secretion and a profound defect in response to T-cell-dependent antigens.[21]

For the first time, CD19 deficiency (*CVID3, MIM#613493*) (Table1) was found in a Turkish girl and three Colombian siblings as a homozygous mutation in the *CD19* gene.[18] The Turkish girl had a homozygous single base pair insertion in exon 6 resulting in a frame shift mutation and premature stop codon in the intracellular part of the molecule. Those three siblings from Colombia were homozygous for a deletion resulting in a premature stop codon in the intracellular domain.[4] In a subsequent report, a Japanese boy was also described to be CD19 deficient with a compound heterozygous mutation in CD19, both of which were novel mutations.[47]

BAFF-R deficiency

BAFF-R is a member of the TNF receptor family that specifically binds BAFF. This molecule is encoded by three exons of the *TNFRSF13C* gene situated on human chromosome 22q13.[48-50] BAFF-R is required for B-cell maturation and survival.[51,52]

Two adult siblings, one with CVID, of a consanguineous marriage have been reported by Warnatz *et al*. in 2009 that carrying a homozygous 24 bp in-frame deletion in exon 2 of the *TNFRSF13C* gene.[20] One sibling (the brother) had decreased IgG and IgM levels but normal IgA and the other (the sister), who was clinically normal, had a slightly diminished IgG and IgM levels in her serum.[4] In other studies, heterozygous sequence variations in the BAFF-R gene (*CVID4, MIM#613494*) (Table1) have been reported.[53]

CD20 deficiency

CD20 in human is encoded by the *MS4A1* gene and is belonging to membrane-spanning 4A (MS4A) gene family.[54,55] This molecule is one of the first B-cell specific differentiation antigens, which was identified from early pre-B until mature B-cell stage during B-cell development.[56,57]

In 2010, Kuijpers *et al*. reported a homozygous mutation in CD20 gene (*CVID5, MIM#613495*) (Table1) in a Turkish girl of consanguineous marriage, with CD20 deficiency. Genetic analysis showed a homozygous mutation in a splice junction of the CD20 gene (MS4A1) resulting in non-functional mRNA variant.[14] The clinical features of this patient presented with hypogammaglobulinemia, decrease in memory B-cells count, recurrent bronchopneumonia and respiratory tract infections from the age of 2.[58]

CD81 deficiency

CD81 (TAPA-1) belongs to the tetra spanning family and forms a complex that signals in conjunction with the B-cell antigen receptor.[59] While CD19 and CD21 are specifically expressed on B lymphocytes, CD81 and CD225 are widely expressed on many immune cell types (T-cells, B-cells, NK cells, eosinophils and monocytes), hepatocytes and most stromal and epithelial cells.[19] This molecule is encoded by the *CD81* gene[60] located on the short arm of human chromosome 11 (11p15.5).[7]

As the first case, Van zelm *et al*. had identified a 6-year-old Moroccan girl born of consanguineous parents. She had CD19 deficiency with a homozygous substitution mutation downstream of exon 6. They showed that defects in the CD19 signaling complex could be involved in development of CVID and even in expression of CD81 on B-cells (*CVID6, MIM#613496*) (Table1) due to the dependency of CD19 on CD81 expression.[19] Her clinical findings were onset of recurrent respiratory infections in early childhood, glomerulonephritis resulting in renal failure and autoimmune thrombocytopenia. She also had impaired antibody response to both pneumococcal antigens and tetanus toxoid. The antibody deficiency pattern was comparable to patients with CD19 deficiency, which was accompanied with reduced $CD27^{+}$ memory B-cells. Somatic hyper mutation was defective through the BCR, particularly in IgA. A decreased IgG level was found in her serum sample, but she had normal IgM and normal to low IgA serum levels.[19]

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CD21 deficiency

Complement receptor type 2 (CR2 or CD21) is encoded by *CR2* gene that situated on human chromosome 1q32.[61] CD21 is a membrane protein on B-cells to which the Epstein-Barr virus binds and infect these cells.[23] This molecule is a member of B-cell co-receptor and expressed by mature B-cells and follicular dendritic cells. CD21 co-receptor on B-cells comforting its activation by recognizing C3d-opsonized immune complexes and enhances antigen specific B lymphocyte responses.[62] CD21 deficiency (*CVID7, MIM#614699*) (Table1) has been described for the first time in a 28-year-old male with mild clinical disorder, born of non-consanguineous parents.[62] On one allele, the patient had a point mutation resulting in one shortened mRNA lacking exon 6. On the second allele, he had a mutation in exon 13, thus creating a premature stop codon at amino acid position 766. Serum IgG and IgA levels were diminished, but the IgG responses to protein and polysaccharide vaccination were acceptable.[4]

Other genetic defects

Mutations, which are reported in the genes encoding for ICOS, TACI, BAFF-R, CD19, CD20 and CD81 account for only less than 15% of CVID cases.[14,16,18-20,38] The remaining 85% of the patients do not have a known genetic defect and it is likely that other genes besides those already identified may be involved in the pathogenesis of the CVID.[63] For example, polymorphisms in genes involved in universal DNA repair machinery (MSH5, MSH2, MLH1, RAD50 and NBS1) and genetic variants of CARD11 and Bob1 genes have also been reported in some patients with CVID.[14-20,63] Nevertheless, none of these genetic defects are yet categorized as an independent syndrome.

Immunopathogenesis of CVID

Th17 cell is a subset of $CD4^+$ helper T-cells and preferentially produce IL-17A, IL-17F, IL-22 and IL-21 upon activation. Retinoid-acid receptor-related orphan receptor C (RORC2) is the specific transcription factor orchestrating Th17 cells differentiation.[13,64,65] Th17 cells and its cytokines are necessary for host defense against extracellular bacterial and fungal infections, but it is mostly known for its role in inflammatory diseases.[13,66] The differentiation and survival of Th17 cells share critical cues with B-cell differentiation and the TFH subset, which was recently shown to be enriched in Th17 cells able to help B-cell differentiation.[67] B-cell differentiation in GCs is required or may contribute to the induction and/or survival of Th17 cells as well.[13] As CVID is defined by impaired antibody production, it is thus reasonable that IL-17 may play a role in this defect.[68-71]

As mentioned before, development and homeostasis of Th17 cells and memory B-cells share several aspects. Tumor growth factor-β is important in isotype switching to IgA[72] and is also essential for Th17 cell differentiation.[73,74] Thus, it is reasonable that the link between B-cell function and IL-17 production may lay on the isotype switching to IgA, an idea which is further supported by the fact that patients with both CVID and X-linked agammaglobulinemia have impaired IgA production.[13] Nevertheless, several studies suggested that the link between B-cells and IL-17 production is not dependent on the development of IgA-producing B-cells.[13] It is not plausible that a unique molecule or pathway determine the impact of B-cells in the homeostasis of the Th17 cells. Involving of several mechanisms either through direct or indirect interactions is more reasonable.[13]

Th17 cells abundantly produce IL-21 as well, which plays an important autocrine role in their differentiation and maintenance.[75] IL-21 which is shown to be involved in Th17 cell development,[73,74] was first described as a critical cytokine in the regulation of antibody production.[76,77] Cytokine IL-6, a major factor for the development of Th17 cells, also plays an important role in B-cell proliferation and antibody production.[78]

BAFF belonging to TNF family (BAFF) is an essential survival factor for follicular B-cells. Increased amount of BAFF may be considered as a determinant for B-cell dysfunction. In one study, a negative correlation is reported in healthy individuals between the frequency of Th17 cells and the serum concentrations of BAFF.[13] This may make stronger the idea of the link between IL-17 production and B-cell maturation.[13]

To evaluate the contribution of B-cells to the Th17 subset, Barbosa *et al*., studied this population in CVID patients as well as in patients with congenital agammaglobulinemia.[13] Their results support a link between the circulating Th17 cells and B-cell differentiation. They found a direct correlation between the frequency of Th17 cells and the frequency of B-cells showing a switched memory phenotype. They showed a decrease in Th17 cell frequency in parallel with the expansion of activated non-differentiated B-cells ($CD21^{low}CD38^{low}$) in CVID patients.[13]

In spite of the decreased Th17 frequency, CVID patients do not show an overt increase in the frequency of infections with *Candida albicans*. This may be due to the preservation of innate producers of IL-17, such as natural killer T-cells, γδ T-cells or innate lymphocyte cells (ILC).[13]

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Innate lymphoid cells are a recently found set of innate lymphocytes discovered at mucosal surfaces. The transcriptional and effector pathways of ILC are strikingly resemble to those of the conventional helper T-cells (Th1, Th2, Th9, Th17 and Th22).[79]

ILCs are concerned in defending the mucosal borders by producing tissue defensive factors.[79] Innate lymphocytes show various effector functions such as restraining the expansion of microorganisms.[80] In contrast with T and B-cells, they act without antigen specific receptors. All ILCs, including LTi, LTi-like, NK22 and $CD4^{-}NKp46^{-}$ cells (except nuocytes) depend on expression of transcriptional regulators, inhibitor of DNA binding 2 (Id2) and retinoid-acid receptor-related orphan receptor gamma t (RORγt).[80] RORγt not only promotes the expression of IL-17 and IL-22 by Th17 cells, but also induces the production of these cytokines by $ROR\gamma t^{+}$ ILCs. This suggests analogous functions of ILCs and Th17 cells during immune responses.[80]

In a more recent study, we found that the overall expression of IL-17 as well as IL-17 producing ILCs count were decreased, while IL-9 was increased in the CVID patients (un-published data). In the context of autoimmune and inflammatory diseases, IL-9 has recently attracted more considerations. IL-9 is mainly considered as an inflammatory cytokine that produce especially by Th9 and Th17 cells.[81]

There are few studies regarding the effect of IL-9 in immunodeficiency, however its role in autoimmune and inflammatory diseases has been more considered.[82] It's reported that increased expression of IL-9 level and high percentages of $CD4^{+}/IL\text{-}9^{+}$ T-cells correlate with more disease activity and severity of systemic lupus erythematosus (SLE) and suggests an important role of IL-9 in the immunopathogenesis of SLE.[83] Moreover, Th9 which characterized by producing a large amount of IL-9, provide important new information on the pathogenesis of autoimmune diseases such as SLE, rheumatoid arthritis (RA) and multiple sclerosis.[84]

Autoimmune diseases are commonly the first manifestation of CVID and affect about 20% of these patients.[68,85] In CVID, the most common autoimmune disorders are hemolytic anemia and thrombocytopenic purpura, but other autoimmune diseases including RA, pernicious anemia, SLE and inflammatory bowel disease have been reported so far.[86] Therefore, IL-9 may be involved in the pathogenesis of autoimmunity in CVID patients.

CONCLUSION

Regarding CVID, a number of genetic defects and immunologic insufficiencies have been described so far. However, the exact immunologic pathways and genetic defects leading to CVID are yet to be clarified. As CVID syndromes are not essentially a group of similar disorders per se and their manifestations are variable from a case to another, more detailed genetic and immunologic studies are required in this context. For example, IL-17 insufficiency in these patients may be due to a defect in Th17 and/or ILC development rising from a defect in RORC2, Signal transducer and activator of transcription 3 (STAT3) and other important molecules in this pathway. More recently, TLRs are getting more attractions in this field. IL-9, as elevates in CVID patients as well as in a number of autoimmune disorders, could be a suitable target for future investigations.

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