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Human B cell defects in perspective

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Abstract

While primary immune defects are generally considered to lead to severe and easily recognized disease in infants and children, a number of genetic defects impairing B cell function may not be clinically apparent or diagnosed until adult life. The commonest of these is common variable immune deficiency, the genetic origins of which are beginning to be at least partially understood. CVID affects $\approx 1/25,000$ Caucasians and is characterized by a marked reduction in serum IgG, almost always in serum IgA, and reduced serum IgM in about half of all cases; these defects continue to provide an opportunity to investigate the genes necessary for B cell function in humans. Recently, a small number of genes necessary for normal B cell function have been identified in consanguineous families leading to varying degrees of hypogammaglobulinemia and loss of antibody production. In other studies, whole-exome sequencing and copy number variation, applied to large cohorts, have extended research into understanding both the genetic basis of this syndrome and the clinical phenotypes of CVID.

Keywords

B cells; CVID; Antibody; Common variable immune deficiency; CD19; CD20; CD21; TACI; Genome-wide study

Primary immune deficiency diseases, now estimated at well over 150 different defects [1], have provided a remarkable resource for investigators in human immunology. With the accelerated pace of work in human diseases, it is clear that many more discrete defects will be discovered in the next few years. Although the first immune deficiencies were described in infants, often males with unusual phenotypes and severe disease, these diseases affect humans of all ages, females and males alike and have characteristic but not necessarily severe consequences [2]. These genetic immune defects are currently categorized into 8 different groups: combined immune defects, other well-described syndromes, defects of the antibody production, immune dysregulation, the innate systems, phagocytes, auto-inflammatory disorders and the complement system. This classification, updated by an expert IUIS panel in 2011, serves as a framework to help in the understanding of various disorders and the diagnostic approach to patients with suspected disease [3]. While novel developments in gene discovery are increasingly apparent, it is also clear that with each iteration, the IUIS classification has become more complex, and in some ways, arbitrary as the emergence of new genes that effect many molecular processes makes it more difficult to assign these to a single classification.

While there have been striking advances in the understanding of these conditions, a number of the commoner immune defects, those which impair B cell function and are often diagnosed in adult life, are still largely uncharted territory. This is somewhat remarkable, considering that about 20 % of the serum proteins are immune globulins which together contain all the antibody species that a human needs to protect against most infections. Aside from the fact that immunizations received in childhood are often sufficient for decades of protection, vaccinations are essential public health strategies against emerging pathogens. In spite of the reliance of the medical field on a healthy humoral immune system, exactly how these large quantities of desirable antibodies are made and continuously replenished, while the production of auto-antibodies is prohibited, remains largely a mystery.

Antibodies that circulate are the end product of an untold number of steps that include continuous reconfigurations of genes for antigen receptors and the elimination of at least 90 % of B cells along the way. Murine models have illustrated the most basic principles of B cell biology, but what is most solidly known for human B cell immunity is based on studies of the primary immune defects [4]. X-linked agammaglobulinemia permitted the elucidation of the X chromosome-encoded cytoplasmic tyrosine kinase Btk, necessary for signaling from the B cell receptor (BCR) and crucial for the maturation of mature B cells [5]. In addition, defects of genes that encode the B cell receptor, the μ chain, Ig alpha chain (CD79a), Ig beta chain (CD79b) and the surrogate light chain lead to loss of B cell development. A mutation in the B cell linker protein (BLNK) similarly leads to agammaglobulinemia and loss of B cell development. The X-linked hyper-IgM syndrome revealed that CD40 ligand is essential to class switch, germinal center formation and the development of B cell memory. Other hyper-IgM defects illustrate the additional requirements for Ig class switch and somatic hypermutation, CD40, activation-induced cytidine deaminase (AID) and uracil-DNA glycosylase (UNG) [6, 7] (Fig. 1).

However, the most common of the B cell defects in humans, the group of diseases known as common variable immune deficiency (CVID), are for the most part not yet well understood from the point of view of pathogenesis, thus providing a still open field for exploration [8]. CVID affects $\approx 1/25,000$ Caucasians and is characterized by marked reduction in serum levels of IgG (usually < 3 g/L) and usually IgA (< 0.05 g/L) with reductions in serum IgM in about half of all cases. With the loss of antibody, patients have a high incidence of infectious disease, leading to sinopulmonary tract infections in particular. For unclear reasons, the immune defects leading to CVID make patients paradoxically prone to both inflammatory and autoimmune disorders [9], which when they appear lead to both increased morbidity and mortality [10].

Even though CVID has been recognized for 6 decades [11], the genetics of this defect have remained unclear. The main reason for this is that family members of CVID patients are most commonly normal, suggesting that complex inheritance and/or other environmental factors are at work. As for other complex immune syndrome, while the hallmark of CVID is the loss of humoral immunity and the World Health Organization classifies this immune defect among the B cell defects, impaired T cell, monocyte and dendritic cell functions have been long described, suggesting that this syndrome bears some resemblance to combined immune defects. In this review, I outline the genes now understood to impair B cell function in humans, with an emphasis on those that allow B cell development but lead to hypogammaglobulinemia and antibody deficiency.

Single-gene approach to CVID

Investigating families with several affected members and consanguineous background, a number of recent reports have extended understanding of these defects and at the same time,

identified the specific roles of genes necessary for normal B cell function. In the first of these, Grimbacher et al. [12] described a homozygous deletion of the inducible costimulator (*ICOS*) gene in four CVID-related patients. ICOS, a cell surface receptor structurally and functionally closely related to CD28 [13], is up-regulated on activated T cells and appears important for B cell activation and the production of IL-10, implicated in the generation of B cell memory and plasma cells [14–17]. Somewhat similar in causality to the X-linked hyper-IgM syndrome which leads to an early immune defect in males, the interaction of ICOS on T cells with ICOS-L on B cells provides T cell help for late B cell differentiation, class-switching and memory B cell generation. The CVID subjects with the ICOS defect had hypogammaglobulinemia and reduced numbers of memory and switched memory B cells [18]. While quite rare, a few other CVID cases with mutations in ICOS have been described [19].

Defects of the B cell receptor signaling and their stabilizing pathways have provided another set of candidate genes. Among these, autosomal recessive mutations in four integral B cell surface proteins (CD19, CD20, CD21 and CD81), each of which forms complexes with the B cell antigen receptor, appear to lower the threshold for B cell activation (Fig. 1). Van Zelm et al. [20] described 4 patients from 2 unrelated families who had hypogammaglobulinemia and mutation of the *CD19* gene, a protein important for stabilizing the B cell receptor [21]. One Turkish patient had an insertional mutation in both alleles of *CD19* leading to a frame shift, while 3 adult, hypogammaglobulinemic siblings from Colombia, were homozygous for a stop codon; in all cases, there were B cells but with a loss of CD19 expression on B cells. While quite rare, a few other cases of CD19 deficiency leading to the CVID phenotype have been described [22, 23]. As the surface receptor CD81 forms part of CD19 functional complex, mutations in CD81 can also lead to hypogammaglobulinemia and impaired antibody production, [24] a situation validated in CD81-knockout mice [25–27]. The gene of a third B cell receptor, CD20, when mutated, similarly leads to loss of B cell differentiation into plasma cells [28], although the mechanisms are somewhat uncertain [29, 30]. The index, and only patient so far, had a homozygous mutation in a splice junction of the CD20 gene resulting in nonfunctional mRNA [31]. CD21, which also augments antigen presentation, when impaired, can also lead to hypogammaglobulinemia. Thiel et al. [32] showed that a 28-year-old male with recurrent infections, reduced class-switched memory B cells and hypogammaglobulinemia had undetectable CD21 receptor expression due to compound heterozygous mutations in *CD21* gene. As for CD19, CD20 and CD81, CD21, also known as CR2 due to its role as a complement receptor, focuses antigen activation on the BCR. While CD21 knockout mice form germinal centers poorly, have short-lived memory cells and exhibit short-lived antibody responses [33], the subject examined had mostly impaired antibody responses to a polysaccharide vaccine. Further advancing this theme of BCR signals, but reflecting the complex nature of signaling intermediates, gain of function mutations in phospholipase C γ 2 was found to underlie a dominantly inherited immune phenotype of cold-induced urticaria with susceptibility to both infections and autoimmunity; some of the affected subjects had impaired antibody production associated with defective B cell calcium flux and isotype switch [34].

Because mice deficient in either BAFF or BAFF-R are characterized by a block of B cell development at the transitional stage [35–40], this was viewed as a logical target for investigation in the search for genes underlying CVID. As BAFF is essential for murine B cell survival [41], initial attempts were focused on identifying both BAFF and BAFF-R mutations in subjects with CVID who had very low B cell numbers. The first mutations noted 3 novel heterozygous variants in *BAFF-R* gene, but these exerted no effect on the expression of BAFF-R both at the mRNA or protein level [42]. Subsequently, Warnatz et al. [43] identified 2 adult siblings (but only one with CVID), born to a consanguineous

marriage, carrying a homozygous deletion in the *BAFF-R* gene, resulting in undetectable BAFF-R expression. However, only one sibling had low serum immunoglobulins (IgG and IgM, but normal IgA) and poor antibody responses to protein vaccines and pneumococcal polysaccharides. The other, who was clinically well, had only a slightly reduced serum IgG and IgM, but preserved antibody production to tetanus, showing that BAFF-R, while perhaps important in some subjects, is not required for B cell survival in humans. No mutations in the *BAFF* gene have been demonstrated.

Even more complex have been the investigations of another TNR receptor, transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) in the study of B cell defects. Activation of TACI, expressed on mature B cells by its ligands, BAFF or APRIL (a proliferation-inducing ligand), leads to T cell-dependent and T cell-independent responses and isotype switch [44–46]. Salzer et al. [47] described mutations in *TNFRSF13B* encoding TACI in 13 mostly adult subjects with CVID. Castigli et al. [48] noted similar findings in a separate cohort and also demonstrated dominant inheritance. In general, mutations in *TACI* are found in about 8 % of CVID patients [49, 50]. The extracellular mutation, *C104R*, and a transmembrane, *A181E*, constitute a majority of mutations identified, with heterozygosity occurring far more common than homozygosity. *C104R* leads to a disruption of a region important for binding the ligands, BAFF and APRIL; the transmembrane mutations lead to impaired BAFF and APRIL signaling. While TACI mutations are significantly associated with the CVID phenotype [50] and in these subjects with both autoimmunity and lymphoid hyperplasia, some of the same mutations can be found in clinically healthy relatives, suggesting the role of other factors [49]. Even homozygous mutations in *C104R* did not lead to hypogammaglobulinemia in 1 of the 3 siblings of a family in which both parents bore one heterozygous mutation [51]. Thus, mutations in *TACI*, while biologically of great interest, are not diagnostic for CVID or predictive of the development of this immune defect.

Larger scale and genome-wide approaches to CVID

A number of earlier studies concentrated on collections of families with both hypogammaglobulinemia and selective IgA deficiency in various members. Vo echovský et al. [52] examined 101 multiple-case families, containing 554 informative family members, and identified susceptibility loci within the HLA region on chromosome 6p sometimes termed *IGAD1*. Of the 110 haplotypes shared by 258 affected family members, a single haplotype accounted for the majority of *IGAD1* contributions to the development of IgAD/CVID in this cohort. Subsequent work also suggested that selected *HLA-DQ/DR* haplotypes conferred either protection or susceptibility to IgAD and CVID [53]. The strong influence of the MHC region has been noted in several other cohorts; in one, the majority of patients inherited HLA *DQ2, *DR7, *DR3 [17], *B8 and/or *B44. B44 was present in almost half and was the most common susceptibility allele [54].

More recently, extensive genome-wide association studies (GWAS) using single nucleotide polymorphism (SNP) arrays have enabled high-throughput genotyping of genomic DNA and investigation of copy number variations (CNVs) in CVID. The first GWAS SNP and CNV study on CVID patients collected investigated 610,000 SNPs of 363 CVID subjects compared to 3,031 controls [8]. Again, a strong association with the MHC region was revealed, and associations with the disintegrin and metalloproteinases 28 (*ADAM28*, *ADAM7*, *ADAMDEC1* and stanniocalcin-1 (*STC1*) were observed. CVID is characterized by fairly stereotypic phenotypic patterns associated with selected inflammatory/autoimmune medical complications [55–60]. Thus, the CVID subjects were classified by these phenotypes, including cancers, lymphoma, lymphadenopathy, nodular regenerative hyperplasia of the liver, lymphoid interstitial pneumonitis (LIP), bronchiectasis, biopsy-proved granuloma, gastrointestinal enteropathy, malabsorption, splenectomy, cytopenias,

organ-specific autoimmunity, low IgM (<50 mg/dL), low IgA (<10 mg/dL), low B cell number (CD19+ cells <1 %) and young age at symptom onset (<10 years) [8]. SNP analysis revealed genes associated with particular phenotypes, including mitogen-activated protein kinase kinase kinase 7-interacting protein 3 (*MAP3K7IP3*) significantly associated with low IgA. Genes significantly associated with lymphoma included *PFTK1*, *HAVCR1* and *KIAA0834*. The gene *CACNA1C* (calcium channel, voltage-dependent, L type, alpha 1C subunit) was found associated with gastrointestinal enteropathy [8].

In addition to SNP investigation, CNV analyses uncovered several novel genes significantly associated with CVID. Of these, 84 CNV deletions and 98 duplications were identified in 1 or more patients but were not found in any of the 2,766 control subjects, some overlapping with the GWAS part of the study. Five deletions and 11 duplications were found to be recurrent in the patient group and were significantly increased in CVID cases compared with controls; 15 regions were unique to CVID cases. Examination of the overall CNV burden of both large (100 kb) and rare (<1 %) CNVs revealed that deletions were significantly enriched in CVID cases, and all but 5 of the 182 CNVs, exclusive to the CVID cohort, were intraexonic [8]. These findings suggest that CNVs may represent alterations in genes that could disrupt normal genetic and/or cellular function in individual subjects with CVID. A second GWAS study of IgAD patients from Sweden and Iceland identified an association with a variant in *IFIH1* and *CLEC16A*, both known to be associated with autoimmune disease, as well as associations with class II alleles in the HLA region [61].

Conclusions

CVID is a complex, multifocal disease, the genetic origins of which are beginning to be at least partially understood. While primary immune defects are generally considered to affect infants and children, a number of genetic defects impairing B cell function may not be clinically apparent or diagnosed until adult life. Further large cohort studies using whole-exome sequencing and other high-throughput methods, along with studies of subjects from diverse genetic backgrounds, will be needed in the future to illuminate the many causes of the CVID syndrome.

Biography

Charlotte Cunningham-Rundles

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Fig. 1. Defects of B cell development and differentiation. The defects that are currently understood to lead to B cell defects are shown in shaded form. BCR is the B cell receptor; TCR is the T cell receptor