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INVITED REVIEW

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Common variable immunodeficiency, cross currents, and prevailing winds

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Summary

Common variable immunodeficiency (CVID) is a heterogenous disease category created to distinguish late-onset antibody deficiencies from early-onset diseases like agammaglobulinemia or more expansively dysfunctional combined immunodeficiencies. Opinions vary on which affected patients should receive a CVID diagnosis which confuses clinicians and erects reproducibility barriers for researchers. Most experts agree that CVID's most indeliable feature is defective germinal center (GC) production of isotype-switched, affinity-maturated antibodies. Here, we review the biological factors contributing to CVID-associated GC dysfunction including genetic, epigenetic, tolerogenic, microbiome, and regulatory abnormalities. We also discuss the consequences of these biological phenomena to the development of non-infectious disease complications. Finally, we opine on topics and lines of investigation we think hold promise for expanding our mechanistic understanding of this protean condition and for improving the lives of affected patients.

KEYWORDS
B-cell tolerance, common variable immune deficiency, dysbiosis, germinal center reaction, T follicular helper cells, T follicular regulatory cells, T regulatory cells

1 | INTRODUCTION

Protein electrophoresis, the centerpiece of the 1948 Nobel Prize in Chemistry, first made it possible to reliably measure serum antibody concentrations.[1] Utilizing this technology, Bruton identified the first sex-linked congenital agammaglobulinemia patients in 1952.[2] Two years later, Sanford, Favour, and Tribeman reported the first case of hypogammaglobulinemia in an adult female, a 39-year-old patient with sinopulmonary infections, autoimmunity, and colitis all beginning in her fourth decade.[3] While such a case was noteworthy at the time, wide adoption of protein electrophoresis as a clinical tool soon made it clear that antibody-deficient adults were more common than congenital patients and their courses were frequently complicated by non-infectious stigmata, including autoimmunity, lymphoproliferation, and malignancy.

The landmark 1971 World Health Organization (WHO) Report on Primary Immunodeficiencies divided known affected patients into 1 of 15 distinct categories, with a "variable Immunodeficiency (common, largely unclassified)" group included as a coda at the list's end.[4] This final category was intended to represent a "work in progress" which encompassed several poorly defined humoral phenotypes. The report's authors envisioned variable immunodeficiencies would be further disentangled through future scientific inquiry. Over the next 50 years, an array of researchers took up this challenge and defined hundreds of distinct inborn errors of immunity, including monogenic forms of agammaglobulinemia, immunoglobulin class-switching disorders, combined immunodeficiencies and immune dysregulatory diseases that were all originally categorized as "variable immunodeficiency (common, largely unclassified)". What remains today, after decades of incremental refinement, is a

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heterogenous group of delayed-onset, humoral diseases collectively called common variable immunodeficiency (CVID).

Given implicit variability, what unifying biology defines the CVID disease category? In the authors' opinion, the central feature is defective germinal center (GC) production of isotype-switched, affinity maturated antibodies. Despite a focus on antibodies and antibody-producing cells, GC defects causing CVID need not be B-cell intrinsic. Aberrations in T follicular helper (Tfh) cells, T follicular regulatory (Tfr) cells, or antigen-presenting follicular dendritic cells (FDCs) have all been described. Importantly, deficiencies of class-switched antibodies are features of many immunodeficiency diseases, but CVID is distinct from congenital agammaglobulinemia, for instance, by the presence of circulating mature peripheral B cells. CVID is also distinct from combined immunodeficiencies (CIDs) by the absence of opportunistic infections. Although CID and CVID may share Tfh and T regulatory cell (Treg) defects, other T-cell subsets (e.g., Th1, Th2, and cytotoxic T cells) affected by CID should not be significantly altered in CVID patients. If they are, alternative explanations should be sought.

The other indelible feature of CVID is phenotypic variability, a predictable consequence of the historical decision to attach a single diagnosis to a somewhat amorphous phenotype. As a practical matter, grouping loosely related patients together does likely improve their collective chances of receiving a timely diagnosis, since clinicians tend to consider the common before the rare, and speeds initiation of antibody replacement therapy. One obvious downside to the "one size fits all" classification is creation of variable patient outcomes, differential responses to therapies, and divergent natural histories.[5] Like the gusts and rough seas that influence a sailing ship's course, the CVID disease category is now pushed from multiple, and often opposing directions by heterogenous forces that include the numerous CVID diagnostic criteria currently in use around the world, the diversity of disease-related genetic lesions, non-inheritable epigenetic factors, tolerogenic defects, variable penetrance phenomenon, and the profound inflammatory effects of dysbiosis (Figure 1).

2 | CVID DIAGNOSTIC CRITERIA(S)

How should CVID be diagnosed? Several diagnostic schemes are currently in use around the world.[6] Each classification is based upon recommendations from disease experts, including 1999 guidance from the Pan-American group for immune deficiencies (PAGID) and European Society for immune deficiencies (ESID),[7] a 2014 update from ESID,[8] a 2016 International Consensus (ICON) document[9] and a 2013 group of clinical immunologists from Oceania.[10] All criterion share stipulations that CVID patients should demonstrate: (1) serum antibody deficiencies, (2) poor vaccine responses, (3) exclusion of other causes of immune deficiency, and (4) delayed onset. There are important distinctions between various diagnostic criteria including differential weight put on serum IgM deficiencies, divergence on acceptable ages of onset, and whether asymptomatic people should be considered as affected. Newer diagnostic schemes also incorporate flow cytometric and genetic analyses to predict which CVID patients will experience non-infectious complications and potentially to exclude some patients with combined immunodeficiencies.

From the perspective of researchers, use of multiple diagnostic strategies to enroll study subjects is problematic. For instance, how can we determine if clinical, biological, demographic, and genotypic differences in CVID cohorts across regions or through time are real or simply artifacts of non-standard study inclusion criteria? Wide adoption of a single diagnostic criteria would permit uniform enrollment into a singular, international CVID research cohort. For this purpose, we see several advantages to using the 1999 PAGID/ESID diagnostic recommendations. First, compared with the 13 stipulations recommended by ESID in 2014, the four listed in the 1999 PAGID/ESID recommendations make it, by far, the simplest criteria to operate. Second, the laboratory testing recommended by PAGID/ESID in 1999 is relatively inexpensive, requires only one tube of serum to be drawn, and is available even in many resource-limited environments. If CVID research cohorts are to be representative of the global patient population, we should encourage enrollment

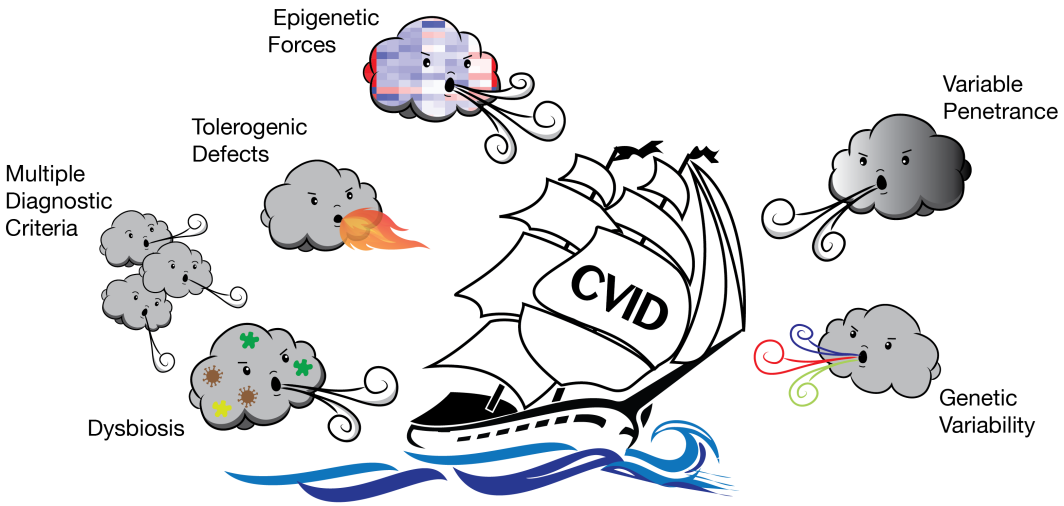

FIGURE 1 The many forces currently increasing CVID heterogeneity are depicted.

outside of academic institutions in developed countries and reduce barriers to enrollment in developing regions.[11] Finally, because the 1999 criteria is the oldest, continuing to utilize it for research purposes offers investigators the best opportunity to compare CVID patient features and outcomes longitudinally.

3 | CVID AS A MONOGENIC DISEASE (OR NOT)

The first description of monogenic CVID was published in 2004; four German patients with homozygous loss-of-function *ICOS* mutations.[12] The discovery of ICOS deficiency was a metaphorical starter pistol that signaled the beginning of an international contest to determine the full genetic basis of CVID. Although the effort has been wildly productive in finding disease-associated genes—by some counts more than 60 have been identified—a genetic diagnosis remains elusive in most patients today. For instance, in our Philadelphia cohort of 161 CVID patients, only 36% carry mutations in one or more CVID-associated genes. In addition to discovering genes, two decades of genetic advances have also unearthed fresh controversies, generated additional points of confusion, and uncovered new, perplexing mysteries in our field.

One current point of confusion and contention is the re-classification of monogenic diseases, originally described in the context of CVID, into other disease categories. For instance, the International Union of Immunological Societies (IUIS) Inborn Errors of Immunity Committee now considers ICOS deficiency a monogenic form of CID, not CVID.[13] The basis for the change was due, in part, to the description of opportunistic infections in a minority of affected patients.[14] Similarly, IUIS now categorizes *LRBA*,[15] *BACH2*,[16] and *CTLA4* defects,[17,18] which were all originally described primarily in CVID cohorts, as diseases of immune dysregulation, due to associated Treg defects. This decision is notable because numeric and functional Treg defects are exhibited by many CVID patients with different monogenic causes (or without one).[19–21] A related, but more semantic controversy, is the recent proposal to exclude patients lacking a molecular diagnosis from the CVID disease category.[22] Under such a regime, a CVID patient could no longer be a CVID patient once a genetic cause was determined. Although we appreciate the importance of clinical genetics, we can enumerate many circumstances in which phenotypic descriptions would aid clinicians and their patients. For instance, CTLA4 loss-of-function (LOF) mutations can be found in multi-system autoimmunity patients who are, or are not, antibody deficient.[23] Only the later presentation would prompt initiation of antibody replacement therapy. CTLA4 LOF mutations can also be found in patients' unaffected relatives who require no treatment at all. For this reason, we advocate for practices that include both genotypic and phenotypic annotations (e.g., CTLA4-haploinsufficient CVID or CTLA4-haploinsufficent inflammatory bowel disease).

A second area of confusion is the phenomenon of incomplete penetrance. Many CVID patients with monogenic forms of CVID have healthy relatives with the same genotype.[24] Penetrance is especially limited for CVID-associated C104R and A181E *TNFRSF13B* mutations which are quite common in the general population; their mean allelic frequencies are 0.003 and 0.005, respectively. Although originally heralded as a monogenic form of CVID,[25,26] it may be more accurate to consider heterozygous *TNFRSF13B* mutations as disease-modifying factors due to their strong association with autoantibody production, especially antibodies causing autoimmune cytopenias.[21,27] Other CVID-associated genes with variable penetrance include those that convey effects via haploinsufficiency (e.g., *CTLA4*,[23] *NFKB1*[28]). In these cases, the transcriptional contribution from the unmutated allele (whether low expressing or high expressing) may be the final determinate of disease state.

Finally, the regularity of mutation-negative disease in the era of whole exome sequencing raises an important existential question: is CVID really an inborn error of immunity? For some, the genetic dark matter behind the majority of CVID cases looms like a specter. Others see opportunities to retrain our focus from the coding to the non-coding genome, which is understudied due to its immense size. One strategy to narrow down non-coding DNA to the regions most likely to affect immune function is creating multi-omic epigenetic maps from relevant tissues, like follicular B and T cells. We have utilized this strategy to successfully identify the distal, non-coding elements regulating immune-associated genes central to lupus and COVID pathophysiology.[29,30] Similar efforts may shed new light on CVID pathoetiology in the future.

It is also possible that a proportion of CVID is caused purely by epigenetic changes. Proofs of this concept are demonstrated by Kabuki syndrome patients who carry damaging mutations in the epigenetic modifying proteins KMT2D and KDM6A. The downstream transcriptional effects of epigenetic alterations are not only responsible for the dysmorphic and developmental features of Kabuki syndrome, but also contribute to humoral immune deficiencies.[31,32] Not all CVID-associated epigenetic changes are the result of germline-encoded defects. Recent, provocative studies profiling the epigenome of monozygotic twins discordant for CVID revealed widespread memory B-cell alterations affecting DNA methylation, chromatin accessibility, and ultimately, transcription of genes associated with BCR signaling, class switching, and chemotaxis.[33,34] The establishment of a CVID-specific methylation signature and the growing means to detect it with technologies like long read sequencing may add additional layers of diagnostic insight when traditional CVID gene candidates remain elusive.

4 | SPECIFIC BIOLOGICAL PHENOMENA CONTRIBUTING TO CVID PATHOPHYSIOLOGY

With or without a known genetic defect, CVID patients display consistent biological features that alone or additively create

characteristic disease phenotypes (Table 1). Prevailing features are described in the following subsections.

4.1 | Primary and secondary B-cell activation defects

Many CVID-associated genes encode proteins involved in B-cell activation including components of the BCR activation complex (*CD19*, *CD20*, *CD21*, and *CD81*),[35–38] signaling molecules downstream of BCR and TLR receptors (*NFKB1*, *PIK3CD*, *PIK3R1*, *PIK3CG*, and *CARD11*),[39–44] and components of the CD40 or APRIL/BAFF signaling apparatuses (*NFKB2*, *TNFRSF13B*, *TNFRSF13C*, *TNFSF13*).[25,26,45,46] Similarly, naïve B cells from CVID patients with and without these mutations demonstrate poor induction of activation markers like CD86 or activation-induced cytidine deaminase (AID) upon BCR or TLR7/TLR9 stimulation.[47,48] Such cell-intrinsic activation defects likely explain why CVID B cells fail to class-switch, affinity maturate, and terminally differentiate into plasmablasts. There are also CVID patients with LOF mutations in genes necessary for T follicular helper (Tfh) cell development (*ICOS* and *ICOSL*)[12,49] that experience B-cell activation defects secondary to poor Tfh help within GCs. Follicular dendritic cells, which are non-hematopoietic presenters of native antigens, may also be affected by CVID-associated gene defects, specifically loss of the complement receptor CD21.[37,50] No matter the cell types ultimately responsible, the common pathway is poorly activated B cells and hypogammaglobulinemia. Although IgG deficiency can be easily remedied through regular IgG infusions, IgA currently cannot. The consequences of stark IgA deficiency include gut dysbiosis, translocation of microbial components (endotoxin, DNA), and resultant systemic inflammation.[51–55]

Not all CVID-associated gene mutations immediately reduce B-cell activation. For instance, CVID-associated gain-of-function *PIK3CD* mutations, or LOF *PIK3R1* and *CTLA4* mutations, promote B- and T-cell lymphoproliferation and autoimmune manifestations. The effect of continuous lymphocyte activation to the patient is reduction of circulating follicular B cells[56] and enrichment of exhausted lymphocytes.[41] One exhausted population studied extensively in CVID patients are $CD21^{lo}$ B cells.[57–59] Expanded in CVID due to activating mutations or due to chronic infectious exposures (or both), these cells appear dependent on interferon-gamma and the transcription factor T-bet.[60] Whether these cells are causes or consequences of antibody deficiency (or both) is unclear, but their presence has been used as part of several flow cytometry-based CVID classification schemes to predict non-infectious complications.[61,62]

4.2 | Impaired B-cell survival

Once B cells egress from the bone marrow, their survival in periphery hinges on the interaction between B-cell activating factor (BAFF) and its receptor (BAFF-R).[63] Deficiency in BAFF-R or its downstream signaling apparatus, such as TWEAK and NFKB2, profoundly impair B-cell maturation. This disruption manifests as an accumulation of transitional B cells and poor memory B-cell generation.[40,45,64] Beyond the CVID phenotype, *NFKB2* mutations can lead to additional complication including autoimmunity, adrenal insufficiency,

TABLE 1 Causes and consequences of CVID pathophysiology.

Biological feature	Molecular mechanisms	Consequences to patients
Poor B-cell activation	BCR defects: *CD19*, *CD20*, *CD21*, and *CD81* mutations BCR/TLR signaling defects: *NFKB1*, *PIK3CD*, *PIK3R1*, *PIK3CG*, and *CARD11* mutations CD40 or BAFF/APRIL axis defects: *NFKB2*, *TNFSF12*, *TNFRSF13B*, *TNFRSF13C*, and *TNFSF13* mutations Defective B-cell help: *ICOS*, *ICOSL*, and *CD21* mutations	Hypogammaglobulinemia Poor vaccine responses
Impaired B-cell survival	CD40/BAFF/APRIL axis defects: *NFKB2*, *TNFSF12*, *TNFRSF13B*, *TNFRSF13C*, and *TNFSF13* mutations	Deficiencies of terminally differentiated B cells
	Transcription regulation defects: *IKZF1* and *SPI1* mutations	Progressive B-cell lymphopenia
Treg dysfunction	CTLA4-related defects: *CTLA4* and *LRBA* mutations Numerical Treg deficiencies: Mechanism unknown	T-cell hyperproliferation and autoimmune disease
Disturbed B-cell tolerance	Central tolerance defects: *TNFSFR13B*, *CD19* mutations and attenuated TLR7 and TLR9 signals	Autoreactive naïve B cells
	Peripheral tolerance defects: Treg dysfunction (see above)	
	Follicular tolerance defects: Attenuated somatic hypermutation and loss of clonal redemption	Autoantibody production
Follicular hyperplasia	Endotoxemia and elevated Activin A production: IgA deficiency and dysbiosis Tfr cell imbalances: Aberrant Tfr cell development	Lymphadenopathy/splenomegaly Elevated cTfh cells Autoantibody production

Abbreviations: BCR, B-cell receptor; cTfh, circulating T follicular helper; Tfr, T follicular regulatory; TLR, toll-like receptor; Treg, T regulatory cell.

and ectodermal dysplasia emphasizing the role of non-canonical NF-kB signaling beyond B-cell biology.[65–67]

B-cell survival defects may also occur later in life, for instance, haploinsufficiency of IKAROS, a key B-cell development transcriptional factor, causes late-onset loss of B-cell mass with resultant hypogammaglobulinemia.[17] Similarly, *SPI1* haploinsufficiency, which we consider a monogenic cause of congenital agammaglobulinemia, has been described in a patient who became B-cell lymphopenic and antibody deficient during adulthood.[68] It is unclear whether these delayed B-cell survival defects stem from decreased transcription factor supplies as patients age or from increased demand.

4.3 | Regulatory T-cell dysfunction

Tregs are critical to limiting inflammation and autoimmunity.[69] One key molecular mechanism Tregs use to exert control is CTLA4. CTLA4 is an inhibitory cell surface receptor that sequesters B7 ligands via transendocytosis to limit effector T-cell coactivation.[70,71] Based on this biology, it is not surprising that CTLA4 haploinsufficient patients develop autoimmune complications such as enteropathy, interstitial lung disease, and autoimmune cytopenias.[17,18,72–74] Less straightforward is the approximately one-third of CTLA4 haploinsufficiency patients who develop recurrent infections and hypogammaglobulinemia.[72] One possible explanation for the observed antibody deficiency is the essential role of CTLA4-sufficient Tfr cells in orchestrating GC responses.[75,76] Further evidence of CTLA4's importance to humoral immunity is provided by patients with homozygous LOF mutations in LRBA, a key recycler of ligand-activated receptors, notably CTLA4.[77] As with CTLA4 haploinsufficiency, LRBA-deficient patients experience polyautoimmunity, with about half displaying hypogammaglobulinemia, fewer class switched memory B cells, and recurrent infections, that is CVID.[15,72,78] Importantly CVID patients with mutations in genes not expressed by T cells, like *TNFRSF13B*, also commonly display numerical Treg deficiencies.[21] Hence, Treg dysfunction may be a common pathologic feature of CVID, not a just a feature restricted to patients with *CTLA4* and *LRBA* mutations.

4.4 | B-cell tolerance defects

Most B cells completing V(D)J recombination are autoreactive and must be counter selected at tolerance checkpoints occurring at discrete development stages. The failure to tolerize B cells conveys significant risks of autoimmunity and is an important mechanism of autoantibody-mediated disease in CVID patients. The central B-cell tolerance checkpoint occurs early in B-cell development within the marrow.[79] Unlike developing T cells, which uses medullary thymic epithelial cells to determine self-reactivity, developing B cells rely solely on the signal strength of their own BCR and the presence of TLR7 and TLR9 coactivation signals.[80] Proofs of this concept are the autoreactive BCRs expressed by early B cells from BTK-deficient agammaglobulinemia patients, and from CD19-deficient CVID patients.[81,82] Similarly, early B cells from IRAK4 and MyD88 deficient patients, which cannot sense TLR ligands, are more likely to express anti-nuclear BCRs.[83] Moreover, early B cells with mutations of TNFSFR13B, a cytokine receptor that enhances both BCR and TLR signaling, are both broadly autoreactive and recognize anti-nuclear antigens.[21,84] Not surprisingly, CVID patients carrying *TNFSFR13B* mutations are at higher risk of autoantibody-mediated cytopenias due to defective central B-cell tolerance.[27]

A second B-cell tolerance checkpoint occurs in the periphery before B cells find their cognate antigen and enter the GC reaction.[80] In the periphery, B cells interact with T cells, including FOXP3-expressing Tregs, which appear integral to a peripheral tolerance checkpoint. Indeed, early B cells are tolerized in the marrow of FOXP3-deficient patients with immunodeficiency polyendocrinopathy enteropathy X-linked patients, but mature naïve B cells are enriched in self-reactive BCRs.[85] Further enrichment of autoreactive mature naïve B cells also occurs in CVID patients with *TNFSFR13B* mutations who exhibit quantitative and qualitative Tregs defects. In contrast, the central tolerance defect of immunocompetent relatives carrying the same *TNFSFR13B* mutations is largely corrected by intact peripheral tolerance mechanisms anchored by functionally suppressive Tregs.[21,84] The precise anatomic site where peripheral B-cell tolerance occurs remains unclear.

A final B-cell tolerance checkpoint occurs within GCs and is mediated by somatic mutation. In a process first observed in immunized mice and named clonal redemption, autoreactive BCRs are first somatically mutated away from self-recognition before adding protein-altering mutations that increase high-affinity interactions with the vaccinating antigen.[86,87] There is evidence that clonal redemption is also an important mechanism for human B cells to tolerize self-reactive immunoglobulin heavy chains encoded by the gene segment VH4-34.[88] In healthy donors, most class-switched memory B cells utilizing the VH4-34 gene segment carry amino acid-altering mutations at sites mediating autoantigen recognition. In CVID patients with autoimmune cytopenias, VH4-34 utilizing class-switched memory B cells are unmutated at these sites, likely explaining their auto-antibody-mediated cytopenias.[88] Hence, the key immunologic features of CVID, which include defective BCR/TLR activation, Treg function, and somatic hypermutation, interfere with all described human B-cell tolerance mechanisms.

4.5 | Aberrant GC dynamics, insights from CVID lymph nodes

The lynchpin of humoral immunity is the GC reaction, a specialized structure that coordinates interactions between FDC, Tfh, and GC B cells.[89] Although many CVID diagnostic criteria, like serum antibody concentrations, vaccine responses, and class-switched memory B-cell frequencies, are indirect measures of GC output, the structure itself is rarely visualized in affected patients. Over many years, we have collected malignancy-free excisional lymph node biopsies from

CVID patients undergoing staging for breast cancer or to evaluate for lymphoma. Analysis of these tissues revealed that CVID GCs can be either diminutive or exuberantly hyperplastic and asymmetric. Correlation of these tissues with paired blood samples revealed that patients with hyperplastic GCs have the lowest serum IgA concentrations, the highest serum endotoxin concentrations, and invariably experience non-infectious complications, specifically autoimmune cytopenias.[54,90,91] In contrast, patients manifesting only sinopulmonary infectious complications primarily display hypoplastic GCs (Figure 2).

We also determined that components of hyperplastic GCs may circulate in the peripheral blood of CVID patients. Numerous studies have observed increased frequencies of circulating Tfh cells (characterized as memory CXCR5$^+$PD1$^+$ CD4 T cells) in CVID patients with non-infectious complications.[21,90,92] Our data show that circulating Tfh frequencies were the highest in CVID patients with hyperplastic GCs but this rise was not accompanied by a concurrent increase in GC reactions' chief products: class-switched memory B cells and vaccine-specific antibodies.[54] Of the few IgG$^+$ memory B cells circulating in the blood of CVID patients with non-infectious complications, there was almost no evidence of affinity maturation.

4.6 | Expansion of circulating Tfh cells

Why do CVID patients with non-infectious complications have so many cTfh cells? One possibility is that they are expanded by dysbiosis-associated systemic inflammation. In a series of in vitro Tfh differentiation experiments, we previously reported that healthy donor naïve CD4$^+$ T cells were twice as likely express the canonical Tfh markers CXCR5 and PD1 if cultured in plasma from CVID patients with non-infectious complications than if cultured in plasma from healthy donors or CVID patients without non-infectious complications.[53] Interestingly, the addition of endotoxin-neutralizing polymyxin B counteracted the Tfh-promoting effect of CVID plasma whereas spiking lipopolysaccharide (LPS) into plasma-free cultures recapitulated it. A second possible reason for cTfh cell expansion in CVID patients is activin A, known to be a powerful inducer of Tfh differentiation.[93] Indeed, plasma activin A concentration and cTfh frequencies correlate closely in humans with and without CVID.[53,94] Since activin A is released from LPS-activated myeloid cells,[95] endotoxemia may represent a common, upstream regulatory signal alerting the humoral immune system that GC output is insufficient to restrain microbial translocation (Figure 2). In the immunocompetent, the endotoxin signal may prompt Tfh expansion to increases GC activity and augment antibody production. In CVID patients, endotoxemia may act as a chronic, unopposed Tfh expanding signal that cannot be quenched due to B cell-intrinsic defects impairing IgA production at mucosal barrier sites. Antibody replacement therapies currently in development containing IgA and/or IgM, which can both be transported into the gut lumen via their J-chain, may directly address this problem.[96,97]

Circulating Tfh cells can be delineated into cTfh1, cTfh1/17, cTfh2, and cTfh17 subsets based upon expression of master transcription factors and/or cytokines/chemokine receptors.[98] Tfh subsets from healthy donors are demonstrably unequal in their ability to promote B-cell class-switching and plasma cell differentiation. Circulating CXCR3$^+$ Tfh (cTfh1) cells from healthy donors primarily secrete IFN-γ and are particularly poor B-cell helpers.[98,99] Our group and others have shown that circulating CXCR3$^+$Tfh cells predominate in CVID patients with non-infectious complications.[53,100,101] A provocative 2016 study of European CVID patients established a correlative relationship between the frequency of cTfh cells expressing CXCR3 and increased patient serum IFN-γ concentrations.[101]

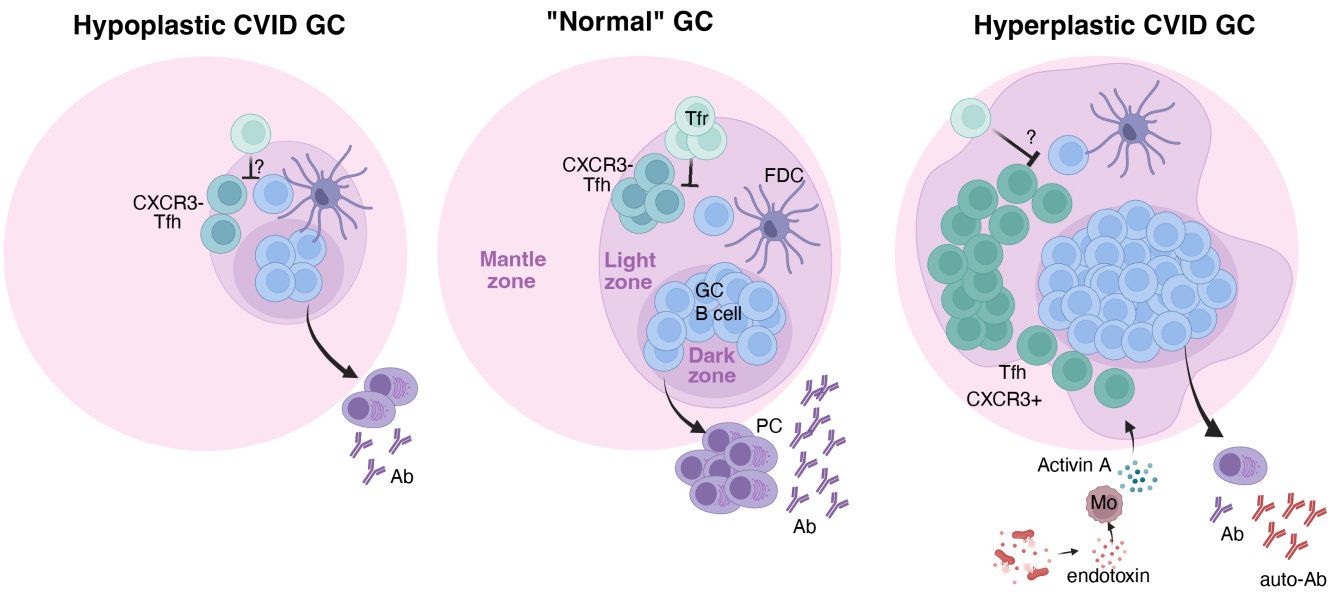

FIGURE 2 The biological phenomena contributing to CVID-associated hypoplastic or hyperplastic GC responses and resultant consequences are depicted.

This work suggested a novel, B-cell independent mechanism for antibody deficiency—the secretion of IFN-γ, not IL-21, by their Tfh cells. To further explore this phenomenon, we analyzed cytokine secretion by CXCR3$^+$ cTfh cells from a group of CVID patients living in the eastern United States who harbored similar gene mutations (e.g., *NFKB1*, *CTLA4*, and *TNFRSF13B*) to their European counterparts. Although >90% expressed surface CXCR3, our patients' cTfh cells predominately produced IL-21, not IFN-γ.[53] Moreover, sorted cTfh cells from our study's patients were able to effectively compel healthy donor naïve B cells to class switch and secrete antibodies in vitro. In contrast, neither healthy donor nor CVID cTfh cells could effectively activate CVID naïve B cells in co-cultures. More recently published results of a different CVID cohort from the western United States corroborate our findings: namely that CVID cTfh cells are effective B cell-helpers despite high CXCR3 expression.[102] Altogether, this body of work indicates that although serum IFN-γ concentration may be elevated in some CVID patients, CXCR3$^+$ cTfh cells are not necessarily its source, nor are they the most likely explanation for hypogammaglobulinemia.

4.7 | Tfr cells, the final arbiters of GC output?

What keeps GC reactions trained on microbial antigens in healthy donors and why do CVID patients generate autoantibodies but not vaccine titers? One possible explanation is disease-associated differences in Tfr cells. Tfr cell-deficient mice not only develop autoantibody-mediated diseases but also fail to affinity maturate immunoglobulins to recognize vaccine antigens,[103] a phenotype similar to CVID patients with non-infectious complications. Two research groups have recently compared the frequencies of circulating cells with a CXCR5$^+$CD25^{hi}CD127^{lo} Tfr cell phenotype in CVID patients to counterpart cells in healthy donors. Both studies noted a marked reduction in CVID cTfr cells but the loss was not greater in patients with non-infectious complications.[100,102] Our own work on this topic found that CXCR5$^+$CD25^{hi}CD127^{lo} cells from CVID patients with autoimmune cytopenias were not only lower but also contaminated by a non-suppressive FOXP3$^-$ population.[53] Hence, scarcities of bona fide FOXP3$^+$ cTfr cells may predict non-infectious CVID complications and a poor disease prognosis.

Recently, we analyzed tissue-resident Tfr cells from immunocompetent donor tonsils using a multi-omic suite of tools (CITE-seq, paired TCRab-seq and high-dimensional microscopy) and in vitro modeled our findings with tonsillar organoids.[104] Our data revealed that the tonsillar Tfr cell pool is comprised of two distinct lineages: one derived from Tregs (natural Tfr or nTfr cells) and the other originating from Tfh cells (induced Tfr or iTfr cells). Although both Tfr subsets expressed FOXP3, they were functionally distinct, resided in different parts of the follicle, and expressed distinct TCR specificities. Our work indicates that nTfr cells primarily reside in the follicular mantle, recognize the same antigens as Tregs, and provide elite suppressive function. In contrast, iTfr cells reside within the GC, recognize the same antigens as Tfh cells, and are capable of GC B-cell help. We have not yet had the opportunity to enumerate Tfr cell subsets in CVID patient lymph nodes but nTfr/iTfr imbalances might explain why some patients favor production of self-reactive, rather than vaccine-recognizing, antibodies.

5 | CONCLUSIONS

Herein we detail the current state of CVID as a clinical and a scientific entity from the perspective of a clinical/translational immunologist and a basic/translational immunologist based in the United States and France, respectively. The review comes 20 years after the initial report of ICOS deficiency, and a decade of whole exome sequencing thousands of CVID patients around the world. Much was learned through these efforts, including the important realization that not all CVID cases can be explained by rare, protein-altering mutations in immune genes. We reviewed the other biological contributions to CVID immune physiology and described key sources of disease heterogeneity. Some variables, like the multiple CVID diagnostic criteria currently in use, seem avoidable through consensus seeking efforts. Additional variety, for instance regional differences in human genetics, commensal microbiota, and pathogens, could be addressed by more inclusive enrollment of patients living in underrepresented, resource limited settings. Other variables, like the epigenetic phenomenon causing monozygotic twins to be discordant for CVID, are only now coming into focus.

Where will the next advances in our field come from? Fresh insights may be hiding in historical blind spots like the tendency to study patient peripheral blood samples, not tissues, and to primarily focus attention on hematopoietic cells. Although other medical subspecialities commonly biopsy diseased tissues to aid in diagnosis or to gauge therapeutic responses, clinical immunologists rarely excise or request excision of lymph nodes from CVID patients. It is disappointing researchers lack access to the very tissues in which most CVID immunopathology is centered. Of available nodes, the majority are removed to evaluate for CVID-associated lymphoma. Accordingly, even if malignancy-free, most tissues are grossly enlarged and exhibit follicular hyperplasia. Our group has had rare success in obtaining less reactive, cancer-free lymph nodes from CVID patients undergoing breast cancer staging surgeries, but this strategy introduces several confounding variables, most notably gender, age, and cancer diagnosis. The best possibility, although fraught with logistical and ethical considerations, would be to sample draining lymph nodes from patients at set timepoints after vaccines were administered to ipsilateral limbs, to define response, and contralateral limbs, as controls. Given the limited material available, future efforts to analyze excised tissues from CVID patients should be collaborative across centers and ideally create spatially resolved, multi-omic datasets to be deposited in public repositories for widest use and greatest good. Another promising approach now in use is modeling GC defects in vitro using tonsil organoids.[105] Unfortunately, tonsil

organoids prepared using recently published protocols contain few stromal cells and therefore may not be appropriate to model CVID FDC defects. The contribution of stroma to inborn errors of immunity is generally understudied to the detriment of affected pateints.[106] After all, neither of the two main therapeutic levers available to clinical immunologists, antibody replacement therapy and hematopoietic stem cell transplantation, addresses stromal defects.

As parting words, we note that clinical immunologists seem forever at cross-roads between our desire to deeply understand disease mechanisms at the single nucleotide level, and practical matters like timely diagnosis or effective treatments. This is especially true when caring for CVID patients who we believe should receive comprehensive genetic testing despite the relatively low odds of identifying a causative gene mutation. It is also reflected in the growing array of advanced methods that researchers employ to study the CVID immune system (e.g., flow cytometry, epigenetic profiling, plasma proteomic analyses, and single cell transcriptomics) even though our findings tend to confirm results of simpler, more widely available, serum antibody tests. Finally, we have never had a better appreciation for the many genetic, epigenic, and non-genetic differences between different types of CVID yet still we treat all patients with virtually the same backbone of antibody replacement therapy.

Given these apparent contradictions, why should we continue studying the biological phenomenon called CVID? The best answer is to improve outcomes for patients with and without monogenic causes. After years of despairing over the differentially worse survival of CVID patients with non-infectious complications, we finally find ourselves with therapies that modify their prognosis.[107,108] In the last decade, off-label use of CTLA4-Ig has added much needed regulatory muscle to CTLA-4 haploinsufficient and LRBA deficient immune systems.[73,74] More recently, JAK inhibitors have returned equilibrium to an ever-enlarging list of STAT and JAK gain-of-function mutations.[109–111] For hyperproliferative defects, sirolimus has become a therapeutic mainstay joined in 2023 by leniolisib, a PIK3CD inhibitor, approved by the US Food and Drug Administration under orphan drug and rare pediatric disease designations.[112] Although each therapy listed above has a different mechanism of action, each success follows the same winning blueprint: (1) understand human diseases by studying human patients, (2) identify disease mechanisms that harm patients, (3) target harmful pathways, preferably through repurposed therapies, and (4) repeat.

AUTHOR CONTRIBUTIONS

Neil Romberg and Carole Le Coz conceived and wrote the article together. Both authors approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable as no new data were generated.

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