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IMMUNE DEFICIENCY AND DYSREGULATION (DP HUSTON AND C KUO, SECTION EDITORS)

Dysregulation of Innate Lymphoid Cells in Common Variable Immunodeficiency

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Abstract Common variable immunodeficiency (CVID) is the most prevalent symptomatic primary immune deficiency. With widespread use of immunoglobulin replacement therapy, non-infectious complications, such as autoimmunity, chronic intestinal inflammation, and lung disease, have replaced infections as the major cause of morbidity and mortality in this immune deficiency. The pathogenic mechanisms that underlie the development of these complications in CVID are not known; however, there have been numerous associated laboratory findings. Among the most intriguing of these associations is elevation of interferon signature genes in CVID patients with inflammatory/autoimmune complications, as a similar gene expression profile is found in systemic lupus erythematosus and other chronic inflammatory diseases. Linked with this heightened interferon signature in CVID is an expansion of circulating IFN-γ-producing innate lymphoid cells. Innate lymphoid cells are key regulators of both protective and pathogenic immune responses that have been extensively studied in recent years. Further exploration of innate lymphoid cell biology in CVID may uncover key mechanisms underlying the development of inflammatory complications in these patients and may inspire much needed novel therapeutic approaches.

Keywords Common variable immunodeficiency · Innate lymphoid cells · Inflammatory bowel disease · Lung disease · Mucosal immunology

Introduction

Common variable immunodeficiency (CVID) is the most common symptomatic primary immune deficiency with an incidence estimated at 1:25,000, though this can vary in different locations [1, 2]. Importantly, CVID is a heterogeneous disorder of diverse genetic etiologies all leading to a shared phenotype of profound antibody deficiency [3]. While the genetic causes of CVID are known for only a minority of patients, the list of mutations associated with this immune deficiency has been steadily increasing through extensive research efforts [4, 5]. To meet the diagnostic criteria of CVID, patients must have marked reductions of serum IgG, IgA, and/or IgM (conventionally at least two standard deviations below reference levels) along with impaired antibody responses to vaccination, often with extensive reduction of isotype-switched memory B cells [6]. CVID patients typically present with frequent sinopulmonary infections, but autoimmune, granulomatous, and lymphoproliferative diseases occur in a significant proportion [7]. Perhaps due to the heterogeneous nature and somewhat later onset of symptoms than many other primary immunodeficiencies, the diagnosis of CVID is often delayed many years due to poor recognition of the immune defect [8••].

The underlying pathogenesis leading to the immunological findings of CVID is poorly understood. Rare monogenic causes for the disorder have been identified, some instances

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involving genes easily linked to the B cell dysfunction that defines CVID while in other cases the connection to antibody deficiency is less clear [9]. Complicating genetics is that newly described autosomal dominant forms, such as mutations of cytotoxic T lymphocyte-associated protein 4 (CTLA-4), signal transducer and transcription activator 3 (STAT3), and NFκB1 are found in CVID subjects, but sometimes also in asymptomatic family members [10–12]. In other instances, genes such as transmembrane activator and calcium-modulating ligand interactor (TACI) found also in some normal subjects may act as disease modifiers rather than causative mutations [13]. Moreover, CVID is typically diagnosed in adulthood, suggesting a role for the environment, somatic genetic changes, and/or nucleic acid modification. Further research efforts are necessary to adequately understand the biology that underlies CVID and its complications.

CVID mortality has improved in recent decades due to wide adoption of IgG replacement therapy leading to reduction of infections, particularly severe examples such as meningitis, pneumonia, and sepsis [14–17]. Possibly due to this extended longevity, about half of CVID patients now suffer from complications unresponsive to IgG replacement [18]. These "non-infectious" complications are now the most important cause of morbidity and mortality in CVID and include autoimmune, gastrointestinal, and lung disease as well as malignancy [19•]. Treatment of these disorders in CVID is limited because their immunological basis is poorly understood. Simply put, it is not known why all CVID patients share the phenotype of profound antibody deficiency but not all develop these complications. Seeking to understand the reason for this major divergence in the clinical course of CVID, investigators have examined immunologic profiles, clinical phenotypes, cell populations and functions, molecular aspects, and cytokines (as reviewed [20••, 21, 22•]). The wide variability in clinical presentation, combined with the relative rarity of the disease and potential multiplicity of causes, are major hurdles to improve our understanding and develop better therapeutic strategies.

CVID Patients with Non-infectious Complications Have Distinctive Immunological Findings

Extensive work has been done to identify biological features distinguishing CVID patients with non-infectious complications from those without. Impairment of B cell maturation is a feature of many CVID patients, but it is most dramatically affected in CVID patients with these conditions. CVID patients with autoimmunity, granulomatous disease, lymphoid hyperplasia, or splenomegaly have significantly reduced numbers of isotype-switched memory B cells as compared to those without these complications [20••, 23, 24]. Another aspect of B cell dysfunction which specifically characterizes CVID patients with inflammatory complications is increased numbers of circulating CD21 low B cells, found especially in patients with autoimmunity and splenomegaly [25]. This B cell subset has self-reactivity but is apparently anergic and may have expanded in response to persistent antigenic stimulation, as increased numbers of these cells are also found in immunocompetent patients with autoimmune disease or chronic viral infection [26–28]. Autoimmunity, lymphoid hyperplasia, and splenomegaly are also more common in CVID patients with loss-of-function mutations in TACI, a receptor with an important role in B cell regulation [29, 30]. The B cells of these subjects, as well as mutation-bearing relatives, have similar dysfunctions in vitro [31]. Greater preservation of IgM production is associated with lymphoproliferative disease both benign and malignant and may be necessary for the development of at least some autoimmune manifestations in CVID [8••, 32]. In contrast, lower levels of serum IgM are linked with the development of bronchiectasis, a complication of chronic pulmonary bacterial infection [33–38]. While B cell impairment is a key feature of CVID, the mechanisms by which dysfunction of these lymphocytes occurs, and how such dysfunction is connected to the development of non-infectious complications remains to be elucidated.

Additional cellular defects have been identified in CVID over the years; not surprisingly, some of these have particularly associated with autoimmune or inflammatory complications. For example, autoimmunity appears more likely to occur in association with reduction of naïve and regulatory T cells in CVID [39–43]. Numerous defects in cytokine production as well as dendritic and other innate immune cell functions have also been characterized in CVID, potentially leading to the development of inflammatory features in some subjects [22•, 44–46]. Thus, the immune dysregulation underlying non-infectious complications in CVID clearly extends beyond B cell biology.

Interferon Signature in CVID Patients with Non-infectious Complications

A key observation in CVID is the fact that multiple autoimmune and inflammatory complications often occur in the same patient. For example, individual patients commonly have a history of autoimmune cytopenias, lymphoid hyperplasia, splenomegaly, and often granulomatous disease as well [20••, 32, 33]. In the largest retrospective analysis of 2212 CVID subjects, enteropathy was also associated with autoimmunity, granulomas, and splenomegaly, confirming a group of interrelated conditions [47]. This concurrence of complications in CVID hints at shared pathogenesis, or at least divergent effects of the same immunological dysfunction. For example, impaired B cell maturation or regulation, in the setting of lymphoid hyperplasia and loss of tolerance may give rise to autoimmune cytopenias [48–52]. In such patients, the B cell maturation defect could especially impair mucosal antibody

defenses at this microbial interface and thereby predispose to enteropathy [53]. Yet, as mentioned earlier, B cell dysfunction may not be the only contributing factor for the emergence of non-infectious complications in CVID. Patients with mutations resulting in CTLA-4 haploinsufficiency, impairment of function of Fas and its receptor, or STAT-3 gain-of-function have all been linked to the development of autoimmunity, lymphoid hyperplasia, and splenomegaly in antibody deficient patients [10, 11, 54, 55]. Furthermore, association of granulomas with autoimmunity and lymphoid hyperplasia may be explained by the fact that granulomatous inflammation is a common pathology in settings of inadequate antigen clearance and excessive lymphoproliferation. Illustrating this fact, granulomatous inflammation is seen in biopsies of benign lymphoproliferation in patients regardless of a diagnosis of CVID [11, 56–60]. Thus, despite the diversity of conditions that emerge in CVID, unifying forms of immunological dysfunction underlying multiple non-infectious complications are likely.

Categorizing CVID patients into a simplified stratification on the basis of having non-infectious complications or not, our group previously compared the RNA expression profile of whole blood between these two categories of subjects. Interestingly, this study revealed that expression of interferon signature genes was significantly higher in CVID patients with these complications as compared to those without [61••]. While this study demonstrated an increase in the signature of genes common to type I and type II interferon pathways, our follow-up work clearly demonstrated a key role for interferon (IFN)-γ in inflammatory disease [62••]. INF-γ was first recognized for its importance in intracellular pathogen responses and has important stimulatory and modulatory effects upon other immune cells [63]. INF-γ is predominantly produced by conventional natural killer (NK) cells, natural killer T (NKT) cells, as well as effector CD4+ (Th1), and CD8+ (CTL) T cells. Unexpectedly, we found a significant expansion of circulating IFN-γ-producing innate lymphoid cells (ILCs) in CVID patients with non-infectious complications compared to those without and identified these cells in the affected mucosal tissues of these subjects [62••]. Identification of the expansion of ILCs in these CVID patients provided a novel area to further explore in the effort to understand the pathogenesis and clinical course of this primary immune deficiency.

Introduction to Innate Lymphoid Cell Biology

ILCs have recently emerged as innate-like counterparts of T lymphocytes, with similar activity and physiological roles as corresponding T cells [64•]. ILCs lack antigen specificity, produce a milieu of cytokines, and are enriched in barrier sites, such as skin and mucosal tissues. Thus, ILCs are endowed to respond locally and rapidly to environmental changes and act as a first-line modulator of immunity, inflammation, and tissue homeostasis. The ILC family has been divided in three different subclasses, based on shared developmental requirements and effector functions, in many cases mirroring that of effector T cell subsets (Table 1) [65••]. Thus, ILC-1 includes conventional natural killer (cNK) cells, CD127+ ILC-1s, and CD103+ intraephithelial ILC-1 (ieILC-1). cNKs and ieILC-1 have cytotoxic activity, mediated by perforin and granzyme B, while CD127+ ILC-1 have common progenitors and produce IFN-γ [66, 67]. Like Th1 cells, ILC-1 subsets have been implicated in immunity against intracellular bacteria and parasites [68]. ILC-2s are dependent on the transcription factor GATA3 and produce interleukin (IL)-5, IL-13, IL-9, and amphiregulin in response to IL-25 and IL-33 [69]. ILC-2 subsets have been linked to a rapid immune response to helminths and extracellular parasites as well as the development of allergic disease. ILC-3s are the most heterogeneous ILC group, yet they all share the necessity for the retinoic acid-related orphan receptor (ROR)γt, while further subdivided by their surface markers and transcription factor dependency [70]. Human ILC-3s have been shown to produce mainly tumor necrosis factor (TNF)-α, IL-22, IL-17, and in some cases IFN-γ.

Despite the established delineation of ILC subsets, these cells are in fact characterized by a great deal of plasticity, especially between ILC-1 and ILC-3s subsets. It has been shown that in humans, conversion of ILC-3s toward an ILC-1 phenotype is possible upon IL-15, IL-2, and IL-12 stimulation with concomitant inhibition of aryl hydrocarbon receptor signaling [71, 72]. The first study to report such plasticity demonstrated acquisition of T-bet with concomitant loss of RORγt expression in ILCs involved patients with Crohn's disease who harbor an IL-17 and INF-γ producing cell population [73]. In addition, INF-γ producing ILC-1s could be generated in vitro from NKp44+ ILC-3s and ILC-1 cells expand within inflamed Crohn's disease intestinal biopsies in correspondence with a loss of ILC-3 [74••, 75]. The natural cytotoxicity receptor NKp44 belongs to an Ig-like transmembrane activating receptor family on human NK cells, which has been also found in ILC subsets [71]. Expression of T-bet and IFN-γ in ILCs that expressed RORγt appears to be driven by IL-12 and IL-18, as well as, curiously, IL-1β and IL-23 [72, 74••]. This plasticity mirrors that of CD4+ T cells as Th2 and Th17 cells have been shown to acquire IFN-γ productive capacity in response to IL-12 and IL-23 stimulation [76]. The exact sequence of events by which ILC-3 lose RORγt and acquire features typical of ILC-1, such as T-bet expression, is still not fully understood [70].

ILCs and Inflammatory Diseases

As potent cytokine producers ILCs are now appreciated as key drivers of autoimmune and other forms of chronic

Table 1 Types of human innate lymphoid cells (ILCs) and their distinguishing features

ILC type	Sources of activation	Transcription factor	Subtypes	Effector molecules	Role in disease
ILC-1	IL-12 IL-15 IL-18	T-bet	Conventional NK cells CD103+ intraepithelial ILC (ieILC-1) CD127+	IFN-γ NK and ieILC-1: Granzyme Perforin	Immune response against intracellular pathogens and tumors Chronic gastrointestinal and pulmonary inflammation
ILC-2	IL-25 IL-33 TSLP	GATA3		Amphiregulin IL-4 IL-5 IL-9 IL-13	Immune response against helminths Driver of allergic disease and asthma
ILC-3	Aryl hydrocarbon receptor ligand IL-1 IL-6 IL-23	RORγt	Lymphoid tissue-inducer (LTi) NKp44+ T-bet + RORγt + double positive	IL-17 IL-22 LTi: LT-β TNF-α T-bet/RORγt+: IFN-γ	Immune response against extracellular pathogens Disease of gut and skin barrier, including inflammatory bowel disease and psoriasis

IFN interferon, *IL* interleukin, *ILC* innate lymphoid cell, *LT-β* lymphotoxin β, *LTi* lymphoid tissue-inducer, *TNF-α* tumor necrosis factor α, *TSLP* thymic stromal lymphopoietin

inflammatory disease. Indeed, ILC activity is thought to underlie a variety of chronic inflammatory diseases, including inflammatory bowel disease, psoriasis, and rheumatic disease [77–79]. ILCs were first appreciated for their importance in immune regulation at mucosal sites. As such, distinct subsets of ILCs have been described in multiple tissues, particularly the gastrointestinal tract, lungs, and skin (for exhaustive review see [80]). Additionally, a significant role of ILCs is now also appreciated in lymphoid tissues such as tonsil and spleen (reviewed in [66, 81]).

Circulating ILCs may also play a distinct role in immune regulation [82]. It has been estimated that in healthy humans, about 0.01 to 0.1% of circulating lymphocytes express CD127, and most of these cells are ILC-2s [81]. More recently, another study has described a CD117+ circulating precursor for ILC cells in healthy humans [83]. However, it is becoming apparent that in various disease states different ILC subsets are enriched in circulation. Ren and colleagues first described a population of CD3− CD56+ NKp44+ CCR6+ cells reminiscent of ILC-3 with heightened frequency in both synovial fluid and peripheral blood of patients with rheumatoid arthritis [84]. Moreover, these ILC-3-like cells were found to produce IL-22 and TNF-α, which was correlated with disease activity [84]. IL-22 producing ILC-3s have also been described in circulation of patients with psoriasis, compared with numbers found in healthy individuals [85, 86]. Moreover, treatment with TNF-specific antibody in one psoriatic patient abrogated disease in association with a disappearance of NKp44+ ILC-3 cells from blood [86]. Similarly, lineage negative ILC-3-like cells have been found to be elevated in untreated multiple sclerosis patients. Interestingly, therapy with the IL-2 receptor antagonist daclizumab not only decreased the numbers of circulating ILCs in this disease but also modified their phenotype toward an immunoregulatory $CD56^{bright}$ NK lineage [87], providing an interesting insight on the plasticity of these cell types as well as their therapeutic potential. A similar population of regulatory $CD56^{bright}$ NKs has been also described in patients with systemic lupus erythematosus, although they did not correlate with disease activity [88]. Another ILC-3-like population has been described in patients with ankylosing spondylitis, a family of arthritis-associated inflammatory diseases. Phenotypically, they were defined as Lyn- RORc- T-bet+ and NKp44+ and capable of producing IL-17 and IL-22. These gut-derived ILC-3 were expanded in circulation, suggesting an active homing axis between the gut and the inflamed joints [89, 90]. Another type of complex and poorly understood autoimmune disease is systemic sclerosis, with patients showing altered frequencies of ILC-3 and ILC-1 in circulation [91], however, the clinical significance of these findings remain unclear.

ILC biology has just begun to be explored in CVID. A small study of 10 patients with CVID found decreased levels of mRNA levels for Th17-related genes, such as *IL17*, *RORC2*, and *IL23R*, which can also be expressed by ILCs [92]. In addition, lineage negative CD127+ CD90+ ILCs were decreased in peripheral blood of patients with CVID; however, no correlation with clinical features was described [92]. A more recent study found a decrease in CD117+ ILCs, mostly ILC-2, in the circulation of patients with CVID [93]. In the latter, patients with a more pronounced reduction of CD117+ ILCs also showed lower numbers of circulating marginal zone-like B cells and increased prevalence of chronic, non-infectious enteropathy [93]. We found an increase in IFN-γ-producing ILCs to be apparent when comparing CVID patients on the basis of

whether or not they had non-infectious complications; those with such complications had increased levels of circulating ILC-3 cells [62••]. The diversity of these results speaks to the well-established heterogeneity of CVID that continues to complicate study of this primary immune deficiency. Further efforts will be needed to elucidate the mechanisms and significance of observations that ILC biology is altered in CVID to better understand how these immune cells influence the progression of this primary immune deficiency.

Our data suggests that ILCs play a prominent role as a source of IFN-γ that may promote the inflammation found in some subjects with CVID [61••]. Another group found that splenomegaly, one of the most common complications of CVID, was associated with an *INFG* polymorphism [94]. Along these lines, we found IFN-γ-expression to be a defining feature of the ILC-3 cells increased in these CVID patients, as cells were CD127+ and expressed intracellular IFN-γ as well as T-bet, the key transcription factor for IFN-γ-production [62••]. These results were similar to the IFN-γ-expressing pro-inflammatory ILC-3 population previously described in mice [67]. Indeed, murine studies have revealed that RORγt + T-bet + NKp46+ ILC-3s lose IL-17 producing capacity in favor of producing IFN-γ and IL-22 [67]. Thus, it is important to appreciate that a subset of ILC-3 cells may be an important source of IFN-γ during disease states, including in CVID.

Future Directions and Therapeutic Perspectives

As earlier mentioned, an upregulated interferon signature characterizes numerous chronic inflammatory diseases as it also does CVID patients with non-infectious complications. Unsurprisingly, the therapeutic potential of modulating this interferon signature has been explored in autoimmune diseases such as Sjogren's syndrome and systemic lupus erythematosus (SLE). Much of this focus has been on type I interferons, but IFN-γ antagonism is considered to have therapeutic potential as well [95, 96]. For example, neutralization of IFN-γ was shown to ameliorate disease in a mouse model of SLE and IFN-γ antagonism was shown to downregulate IFN signature genes in SLE patients [97, 98]. However, downregulation of IFN signature genes mediated by therapeutic IFN-γ antagonism failed to coincide with clinical improvement in patients with discoid lupus [99]. Much work remains to be done in optimizing this therapeutic approach. Treatment that targets both type 1 IFN and IFN-γ signaling, through STAT inhibition or other methods, may be more effective than targeting one cytokine type alone given the redundancy of their effects [100].

ILC-3 cells themselves are also intriguing therapeutic targets in CVID. Some therapy already in use may have underappreciated roles in modulating ILC activity. For example, inflammatory cytokine production by ILC-3 cells is reduced by the immunosuppressant medication cyclosporin A [101]. Therapeutic antagonism of IL-23 may have benefits both by ameliorating the pathogenic effects of this cytokine as well as its role as a stimulus of IFN-γ production and ILC-3 activation [102]. In a short 8-week clinical trial, IL-23 blockade with risankizumab demonstrated efficacy for inducing remission of Crohn's disease [103]. Therapeutic antagonisms of other cytokines, such as IL-1 or IL-6, may also suppress activation and expansion of ILC-3 cells. Alternatively, treatments impairing cell trafficking may have a profound effect on ILC-driven pathology, as these cells mediate much of their effects locally. Along these lines, as ILCs utilize the integrin α4β7 to migrate to the gastrointestinal tract, their depletion from the GI tract may, along with inhibition of T cell recruitment, contribute to the efficacy of vedolizumab in inflammatory bowel disease [104, 105]. Yet, the relative contribution of ILC-3 suppression to overall efficacy seen by these therapeutic approaches remains to be determined.

Numerous unique considerations regarding CVID remain to be understood in the pursuit of improved therapy for these patients. Prospective longitudinal studies of CVID are lacking in order to determine whether IFN signature expression or circulating ILC expansion precedes the development of inflammatory complications. While hematopoietic stem cell transplant (HSCT) has been used infrequently and with high mortality rates in CVID, efficacy has been profound in those that survive the treatment [106]. Thus, future advancements in HSCT patient selection and safety may improve outcomes in CVID and lead to greater usage of such treatment and consequently have effects upon cytokine and ILC dysregulation in these patients. Similarly, advancement of genetic diagnosis and corresponding gene therapy approaches may lead to future usage of this treatment in some cases of CVID. One of the hallmarks of ILCs is their enrichment in mucosal sites, as well as local self-renewal [107]. Thus, ILC reconstitution after HSCT is slow, as chemo and radiotherapy deplete blood ILCs. A study has shown that a circulating ILC-3 population reappeared after both chemotherapy and allogenic HSCT, but whether the contribution to pathogenesis of certain disease states would be ameliorated by such therapy is unknown [82]. The impact of HSCT and gene therapy upon ILC biology and pathogenic activities of these cells may ultimately have significant impact upon the therapeutic course of CVID, but important mechanisms of their pathogenesis remain to be elucidated.

Conclusions

The development of non-infectious complications in patients with CVID remains an enigma. While immunological findings associated with these complications are numerous, the pathogenesis is not clear. Recent identification of an increased

IFN signature distinguishing CVID patients with non-infectious complications provides a promising avenue of further research because this finding is also shared with other chronic inflammatory diseases where it is being explored as a therapeutic target. Increased circulating ILCs were identified in CVID patients with non-infectious complications and may be an important driving force of the IFN signature also found to distinguish these patients. Of particular importance may be ILC-3 as a key source of pathogenic IFN-γ in CVID. Further research is needed to better understand the contribution of the IFN signature and expansion of IFN-γ-producing ILCs to non-infectious complications in CVID and assess their potential as therapeutic targets.

Numerous unanswered questions remain as ripe areas for future research. What is driving this IFN signature and ILC expansion in a subset of CVID patients? Extensive genetic studies of CVID have yet to reveal an explanation of upregulation of interferon genes. Alterations of the microbiota and translocation of bacterial products due to mucosal antibody deficiency of these patients may play a role, but this remains to be shown conclusively [108]. Moreover, how does the observed IFN signature gene dysregulation relate to the profound B cell dysfunction characterizing CVID? IFN has been shown to delete B cells in the setting of viral infection but has also been linked to the development of autoantibodies, so clearer delineation of the impact of IFN, and perhaps IFN-γ specifically, upon B cells remains to be defined [109, 110]. While early reports have hinted at the importance of IFN and ILC expansion for emergence of non-infectious complications in CVID, the area remains in need of greater research efforts in order to progress toward impactful clinical intervention.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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