Autoimmunity is an integral part of immune dysregulation in common variable immunodeficiency (CVID), often presenting as the first manifestation of the disease (Agarwal and Cunningham-Rundles, 2009). In recent years analyses of the immune disturbances have revealed complex dysregulations of the immune system. In parallel, progress in our comprehension of the pathogenesis of connective tissue disorders like systemic lupus erythematosus (SLE) allows for comparison of common roots of human autoimmune (AI) disorders.

This perspective article is an attempt to summarize the factors which contribute to autoimmunity in CVID.

Autoimmune cytopenias are the most common AI manifestations in CVID and the focus of this article. The presentation of AI-CVID patients resembles patients with autoimmune lymphoproliferative syndrome (ALPS) with the coincidence of lymphoproliferation and AI cytopenias (Serei et al., 2006; Weihe et al., 2008). While none of the cellular markers, such as increased double negative T cells or reduced switched memory B cells, helped to distinguish AI-CVID from FAS-ALPS, increased serum levels of soluble Fas ligand, interleukin (IL) 10, and vitamin B12 allowed a distinction between FAS-ALPS and AI-CVID to be made (Ronai et al., 2010). None of the tested CVID patients carried a genomic or somatic mutation in FAS, rendering FAS-ALPS a differential diagnosis. Thus, the reason that lymphoproliferation and autoimmunity are seen together in most of the CVID patients remains obscure. Other causes of ALPS and ALPS-related disorders have not been excluded systematically in AI-CVID.

Other immunodeficiencies strongly associated with AI manifestations comprise immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome, autoimmune polyendocrine syndrome type 1, combined immunodeficiencies (CID) including hypomorphic severe (S)CID variants (Liston et al., 2008), both calcium channelopathies, Wiskott–Aldrich syndrome (WAS), DiGeorge syndrome, Good syndrome, activation-induced deaminase (AID) deficiency, CD25 deficiency, Stat5b deficiency, and cartilage hair dysplasia (Al-Herz et al., 2011).

Most of these immunodeficiencies are associated with (i) disturbed T cell homeostasis, (ii) altered antigen receptor, or (iii) altered cytokine signaling. Aspects relevant in patients with CVID shall be discussed in the following sections.

DISTURBED T CELL HOMEOSTASIS IN AI-CVID

Disturbed T cell homeostasis is a common contributing factor to the development of autoimmunity in different forms of monogenic primary immunodeficiency disorders (PIDs). Several features of disturbed cell homeostasis are also present in CVID. Lymphoproliferation affects mostly CD4 T cells and especially naive CD4 T cells, while CD8 T cells become relatively expanded (Giovanetti et al., 2007). Both CD4 and CD8 T cells are activated as determined by the expression of activation markers and K67. Thymic output was decreased, but K67 expression was particularly strong in naive and central memory T cells, suggesting homeostatic...
In CVID this phenomenon was exaggerated (Kuntz et al., 2011). The severe reduction in naïve CD4 T cells in CVID has been suggested as a criterion for the diagnosis of late-onset CID (LOCID; Malphettes et al., 2009) for resembling the immunological and clinical phenotype of patients with hypomorphic SCID mutations (Eaton et al., 2008; Cassani et al., 2010; De Ravin et al., 2010). Interestingly, the association of CD4 lymphopenia in primary immunodeficiency seems to be stronger with granulomatous inflammatory disease than AI cytopenias (Schuette et al., 2008; Mouillot et al., 2010). IL-7, which has a key role in the expansion of autoreactive T cell clones in the lymphopenic host, was also found to be elevated in a subgroup of CVID patients (Holm et al., 2005). Though increased IL-7 levels were not associated with T cell lymphopenia, they nevertheless correlated with a more frequent incidence of autoimmunity. The regular feedback mechanism of IL-7 regulation seemed to fail in the small group of AI-CVID patients examined. The production of several other cytokines including IL-2, interferon (IFN)-γ, IL-4, and TNFα is altered in some CVID patients, but none of the reported alterations have been examined for their role in eliciting autoimmunity (Fischer et al., 1994; Fritsch et al., 1994; Mullighan et al., 1997). Testing the role of specific cytokines in this setting will be of great interest as it is likely to reveal potential therapeutic targets.

Sewing of CD8 T cells is often more prominent than that of CD4 T cells (Giovannetti et al., 2007). Cytomegalovirus (CMV) causes immunosenescence associated with terminal differentiation of CD8 effector T cell T cells which results in a skewing of the repertoire (Fischer et al., 1994; Fritsch et al., 1994; Mullighan et al., 1997). The testing of the role of specific cytokines in this setting will be of great interest as it is likely to reveal potential therapeutic targets.

Selection, activation, and differentiation of T cells in CVID may also be affected by an impaired response of the T cell receptor after stimulation (Fischer et al., 1994; Boncristiano et al., 2006; Paccani et al., 2005). However, to date, the published investigations neither report an underlying genetic defect nor a correlation between altered T cell receptor signaling and a higher prevalence of autoimmunity. Currently, the only intrinsic T cell defect which causes CVID was found in a total of 11 patients with deficiency of the inducible costimulator (ICOS; Warnatz et al., 2006; Sauer et al., 2012), cytokine disturbance (Setoguchi et al., 2005), and even persistent CD4 lymphopenia itself (Matsuoka et al., 2010) might contribute to the reduction in regulatory T cells. Interestingly, even ICOS deficiency disturbs maintenance and function of regulatory T cell deficiency a crucial element in AI dysregulation which is also common to different forms of immunodeficiency.

**DISTURBED B CELL HOMEOSTASIS IN AI-CVID**

B cell homeostasis is also disturbed in CVID patients. Therefore, reduced switched memory B cell development and the expansion of activated CD21<sup>low</sup> B cells are associated with the manifestation of AI-CVID (Warnatz et al., 2002; Sanchez-Ramon et al., 2008; Isnardi et al., 2010; Boilreau et al., 2011). CD21<sup>low</sup> B cells contain a high proportion of autoantibody clones (Rakhmanov et al., 2009; Isnardi et al., 2010) suggesting a disturbed selection of the B cell repertoire. This may involve defects in central selection for some (Isnardi et al., 2010), but not all patients (Rakhmanov et al., 2009). Several factors have been identified as interfering with B cell selection. Firstly, the signal strength of the BCR itself determines the outcome during selection (Khan, 2009). Several mouse models have demonstrated that alterations in the signaling machinery (Cornall and Goodnow, 1998; Wang and Clark, 2003) and the balance between co-stimulatory (Fedder et al., 1997) and inhibitory co-receptors (Cornall et al., 1998) determine the counter-selection of AI B cell clones. In CVID patients disturbed antigen receptor signaling was described and is discussed below.

Given the negative feedback loop of immune complexes on B cells and plasma cells via the inhibitory receptors (Seite et al., 2010; Baerenwaldt et al., 2011) it is intriguing to speculate as to whether low serum IgG by itself may contribute to antibody-mediated AI cytopenias as one of the first manifestations in AI-CVID. Signaling by FcRIIB inhibits B cell activation and can even induce apoptosis in plasma cells (Xiang et al., 2007). Additionally, a lack of inhibition of monocytes/macrophages by FcRIIB may foster overwhelming inflammatory responses and granuloma formation, a serious clinical problem seen in a subset of AI-CVID patients. Lupus-like disease in FcRIIB-deficient C57BL/6 mice (Rolland and Ravetch, 2008) as well as the increased risk of SLE in homologous carriers of the dysfunctional FcγRIIB I1237T variant (Floto et al., 2005) clearly indicate a crucial role for this inhibitory receptor in the maintenance of humoral tolerance. This hypothesis is supported by the fact that in most CVID patients the initiation of immunoglobulin replacement leads to an amelioration of the bouts of AI-mediated cytopenias.

The other major factors, which contribute to B cell-mediated autoimmunity, are related to survival signals during selection (Cancio, 2004). For B cells, overexpression of B cell-activating factor (BAFF) causes increased survival of autoreactive B cells and overt autoimmunity (Mackay et al., 1999; Thien et al., 2004). It is noteworthy that most CVID patients present with elevated BAFF levels (Kreuzaler et al., 2012). Currently it is unknown whether elevated BAFF levels sustain the expansion of CD21<sup>low</sup> B cells in

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**Note:** The text above is a natural language representation of the document content. It has been formatted for readability and clarity, with some paragraphs split for better presentation. The original content has been preserved as much as possible, including the citation references and formatting of sections. The document discusses the phenomenon of autoimmunity in CVID, focusing on the role of CD8 effector T cells and the potential therapeutic targets. It also highlights the disturbed B cell homeostasis in AI-CVID, including the association with CD21<sup>low</sup> B cells and the role of factors like ICOS deficiency and BAFF overexpression. The text is organized to provide a coherent flow of information, with key findings and references clearly marked.
CVID. The number of circulating CD21low B cells increases in other AI diseases, such as SLE (Wehr et al., 2004), rheumatoid arthritis (Isard et al., 2010), and cryoglobulinemia (Terrier et al., 2011), supporting an association with autoimmunity. In contrast to SLE, where switched memory B cells are relatively expanded and active disease is associated with expansion of circulating plasmablasts (Dorner and Lipsky, 2004), AI-CVID has a more severe reduction in the number of switched memory B cells when compared to other CVID patients. This could represent a disturbed peripheral differentiation and selection. Increased autoimmunity associated with poor germinal center function has also been observed in deficiency of the AID (Hase et al., 2008), but no abnormalities of AID expression or function have been described in CVID at this point.

Of all the genetic mutations which are associated with CVID, AI manifestations are most common in TACI-deficiency (18/50 (36%) vs 112/490 (23%) in wt TACI CVID; Salzer et al., 2009). In particular, heterozygous CI4OR mutations seem to effect a predisposition for autoimmunity (11/20 patients, 55%; Salzer et al., 2009). While partial TACI signals in a heterozygous state may contribute to the survival of autoreactive B cells, a formal proof of this hypothesis is still missing. AI manifestations including glomerulonephritis and vasculitis (interestingly with deposits of IgA) as well as AI thrombocytopenia (AI-TP) have also been described for CD19 and CD38 deficiency, and are possibly related to the disturbed antigen receptor signal in these patients (see also below; van Zelm et al., 2006, 2010b; Vince et al., 2011). The other B cell-intrinsic genetic defects associated with CVID (BAFF-R, CD20, CD21) have not been reported with AI manifestations (Warnatz et al., 2009; Kuipers et al., 2010; Thiel et al., 2011), but to date only single patients have been described for each defect, thus precluding definite conclusions.

In recent years, a B cell population producing IL10 has been described as regulatory B cells (Mauri and Bosma, 2012). Currently, nothing is known about their existence and function in CVID.

DISTURBED ANTIGEN RECEPTOR SIGNAL IN AUTOIMMUNE CVID

Several mouse models of increased BCR signals demonstrate an increased prevalence of AI manifestations (Dorner and Lipsky, 2006). On the other hand, models of decreased TCR signaling can also represent a risk factor for autoimmunity (summarized in Liston et al., 2008). Decreased TCR signals are thought to interfere with negative selection either through a selective or a stronger impact on tolerogenic signals (Liston et al., 2008) thus potentially impairing the generation of regulatory T cells (Liston and Rudensky, 2007). In humans, ORAI (Fiske et al., 2006) and Stim1 deficiency (Picard et al., 2009) need to be mentioned as prototypical of reduced antigen receptor signal strongly associated with the coincidence of immunodeficiency and autoimmunity in the affected patients. Also in B cells of the subgroup of CVID patients with an increased risk of AI manifestations, calcium signaling is reduced compared to other CVID patients and healthy controls (Fierer et al., 2010; van de Ven et al., 2011). The exact mechanism of the signaling defect and its potential interference with selection are unknown. In WAS, antigen receptor signaling is impaired due to mutations in the WAS protein (Zhang et al., 1999). Interestingly, WASP deficiency also leads to increased AI disease associated with decreased CD27+ memory B cells and increased CD21low B cells (Park et al., 2005). Although WASP deficiency affects both T and B cell receptor signaling, B cell-intrinsic defects clearly contribute to autoimmunity in WAS (Recher et al., 2012). As indicated above, previous reports have found disturbed TCR-induced calcium signals (Fischer et al., 1996) in 40–50% of CVID patients but a link to immune dysregulation in the identified patients has not been established.

ALTERED TYPE I INTERFERON SIGNAL IN AUTOIMMUNE CVID

Cytokines have been implicated in AI dysregulation. Type I IFNs are thought to be particularly important as (i) AI reactions are induced in patients after treatment with type I IFNs, (ii) the IFN signature is increased in patients with SLE, and (iii) some chronic viral infections are associated with autoimmunity (Hall and Rosen, 2010). The mechanisms are manifold and include induction of dendritic cell (DC) maturation and increased BAFF production, a positive feed back loop in toll-like-receptors (TLR) 7 and 9 signaling leading to class switched antibody production (Hall and Rosen, 2010).

Type I IFN expression and the induction of AI reactions is closely linked to the activation of TLRs on plasmacytoid DCs (pDCs) and B cells (Green and Marshak-Rothstein, 2011). Different strains of AI prone mice rendered deficient in TLR7/9 or MIF08 expression produce dramatically fewer autoantibodies and develop less severe disease (Green and Marshak-Rothstein, 2011). Surprisingly, however, TLR9 deficiency in the presence of normal TLR7 function reduces only anti double-strain-DNA autoantibody levels, but not other autoantibodies and is associated with a more severe AI disease, suggesting a regulatory role of TLR9 for TLR7-mediated immune disease. In CVID patients, pDC and B cell responses to TLR7 and 9 ligands are impaired (Yu et al., 2012). Subanalysis of the reported data suggests that a subgroup of patients is more seriously affected by reduced TLR signaling. While the authors correlate the reduced function to increased infection susceptibility no correlation to autoimmunity is mentioned.

In summary, autoimmunity is a prominent clinical feature in CVID. Associated factors include disturbed B and T cell homeostasis and selection, altered antigen receptor signals, increased BAFF levels, and possibly altered TLR signaling. Pathogenic mechanisms, however, have not been identified yet on a molecular level. Further research needs to consider established mechanisms in other genetically defined immunodeficiency disorders to unravel the underlying immune dysregulation in CVID. Our improved knowledge will not only steer potential treatment strategies but also our concept of autoimmunity in general.
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