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Review

Autoimmunity and infection in common variable immunodeficiency (CVID)

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ABSTRACT

Common variable immunodeficiency (CVID) is a heterogeneous group of diseases, characterized by primary hypogammaglobulinemia. B and T cell abnormalities have been described in CVID. Typical clinical features of CVID are recurrent airway infections; lymphoproliferative, autoinflammatory, or neoplastic disorders; and autoimmune diseases among which autoimmune thrombocytopenia (ITP) is the most common. The coexistence of immunodeficiency and autoimmunity appears paradoxical, since one represents a hypoimmune state and the other a hyperimmune state. Considering both innate and adaptive immune response abnormalities in CVID, it is easier to understand the mechanisms that lead to a breakdown of self-tolerance. CD21^{low} B cells derive from mature B cells that have undergone chronic immune stimulation; they are increased in CVID patients. The expansion of CD21^{low} B cells is also observed in certain autoimmune diseases. We have studied CD21^{low} B cells in patients with CVID, CVID, and ITP and with ITP only. We observed a statistically significant increase in the CD21^{low} population in the three pathological groups. Moreover, we found statistical differences between the two groups of CVID patients: patients with ITP had a higher percentage of CD21^{low} cells. Our data suggest that CD21^{low} cells are related to autoimmunity and may represent a link between infection and autoimmunity.

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1. Introduction

Common variable immunodeficiency (CVID) is considered a heterogeneous group of primary immune deficiency diseases characterised by reduced serum levels of IgG, IgA, and/or IgM, with decreased antibody production and impaired antibody response to both polysaccharide and protein antigens. Because of low antibody levels, most patients have recurrent respiratory tract infections. The diagnosis of CVID is an exclusion diagnosis: according to the ESD/PAGID criteria, CVID is considered probable in patients who have marked decrease in IgG levels (at least 2 SD below the mean for patients' age) and marked decrease of at least one of the isotypes IgM or IgA, plus (a) onset of immunodeficiency after 2 years of age, (b) absent isohemagglutinins and/or poor response to vaccines, and (c) exclusion of other defined causes of hypogammaglobulinemia such as drugs, infections, malignancy, genetic disease, protein loss, or hypercatabolism [1,2].

CVID is a rare disease even if it is the most common primary immunodeficiency seen in clinical practice and this is the reason why it is called "common." Estimated CVID incidence in Europe and North America ranges between 1:10,000 and 1:50,000 and the prevalence ranges from 0.073 to 0.0977 living patients per 100,000 inhabitants [3]. These data are underestimated because most physicians are not familiar with CVID, possibly because it is generally thought that primary immunodeficiencies are more common in the paediatric age, while

the onset of CVID manifestations usually is between the second and fourth decades of life. Moreover, CVID symptoms can be quite heterogeneous, inducing the patients to seek for different specialists in otorynolaryngology, respiratory medicine, gastroenterology, rheumatology, oncology, or others. On the other hand, in about 20% of patients, the first manifestation of CVID is not represented by infection but by inflammatory, autoimmune, or neoplastic diseases, hence the word "variable."

2. CVID and immune defects

The typical defect of CVID is the failure of B lymphocytes to differentiate into switched memory B cells and into plasma cells [4] (Fig. 1). During the different steps of their maturation, B cells circulate between splenic follicles, lymph nodes, and bone marrow, until they undergo apoptosis or are activated by an antigen. This allows naive B cells to complete their maturation process to switched memory B cells. Many causes, most of them unknown, can alter this complex process.

In the last 10 years, by genome association studies and genome or exome sequencing techniques, researchers have identified several rare monogenic disorders with a CVID-like phenotype. Defects have been reported in the genes encoding for B cell antigen receptor associated complex (CD19, CD81, and CD21) [5–7], CD20 [8], inducible co-stimulator (ICOS) [9], B cells activating factor receptor (BAFF-R) [10], and transmembrane activator calcium-modulator and cyclophilin

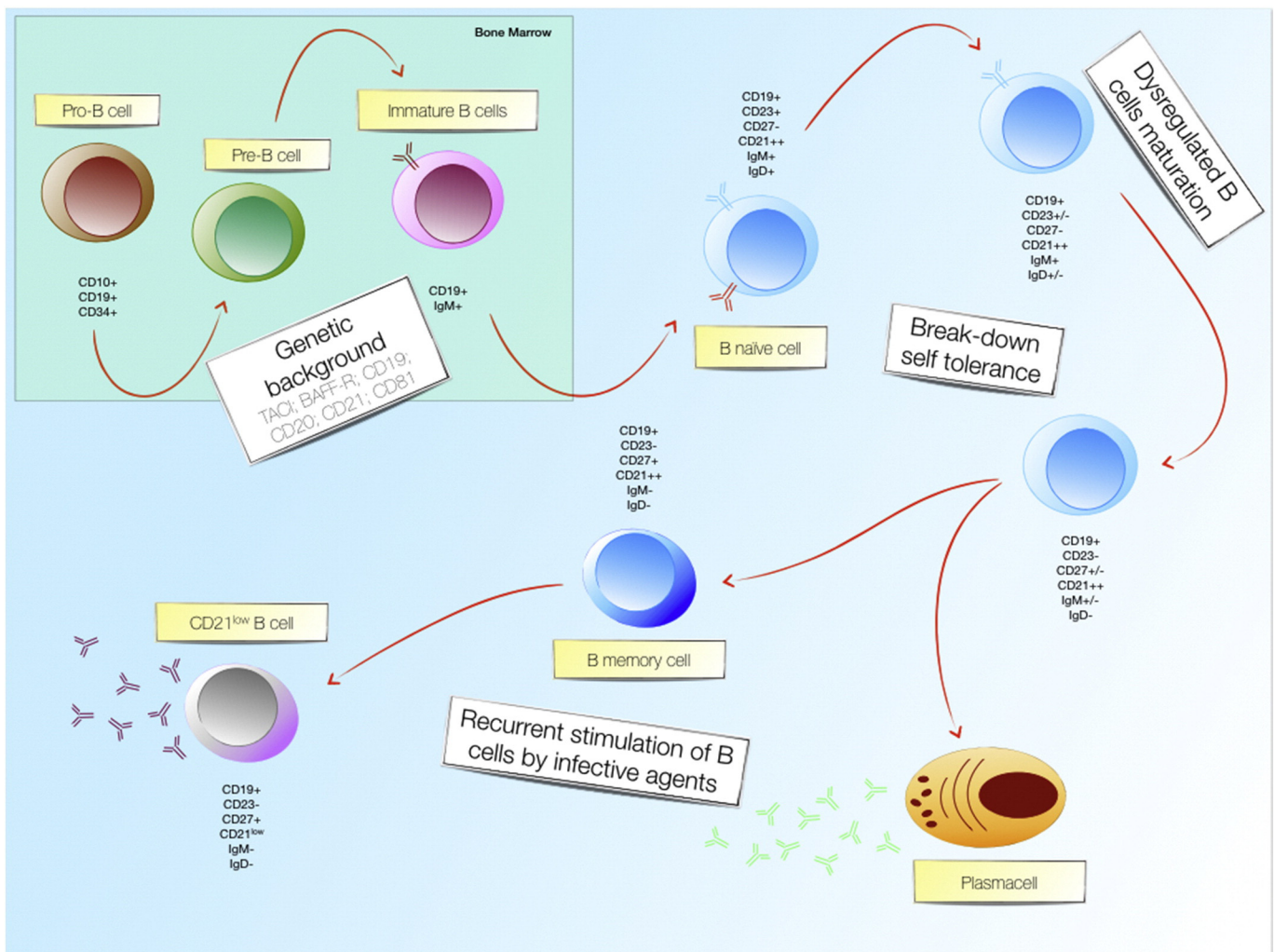


Fig. 1. Dysregulation of B cell development, autoimmunity and recurrent infections in CVID patients. Possible generation of CD21^{low} B cells from memory B cells following recurrent stimulation by infectious agents (see text for explanation).

ligand interactor (TACI) [11]. Nevertheless, these defects have been identified in less than 15% of patients [12,13].

We have reported that centroblasts (IgM + IgD–CD23–CD27–B cells) are increased in CVID patients, while switched memory (IgM–IgD–CD23–CD27–) B cells are decreased suggesting that one of the defects in B cell maturation in CVID patients lies at this step of B cell maturation [14]. Moreover, alterations of the somatic hypermutation process both in the Ig(V) regions and in the light chains have been described in CVID, indicating alterations in B cell maturation in the germinal center [15].

The reduction of switched memory B cells is associated with CVID, although it is not specific since a low number of switched memory B cells has also been found in other primary immunodeficiencies [16]. Interestingly, switched memory B cells develop in the germinal centre of lymph-node in a T-dependent manner. Therefore, their reduction could depend on functional defects in both B and T cells.

Several abnormalities of T cells have also been described in CVID including oligoclonal expansion of CD8 + T cells, decreased numbers of CD4 + T cells [17], T cells activation defects, apoptosis and anergy [18], impaired proliferation in response to mitogens [19], disruption of CD4 + and CD8 + TCR repertoire, reduction of CD31 + recent thymic emigrants CD4 + T cells [20], reduced expression of CD40L on activated T cells, and low levels of IL-2 mRNA [21]. Moreover, T lymphocytes show an impaired secretion of several soluble mediators [22], which may contribute to the B cell differentiation failure.

Finally, the frequency and suppressive function of regulatory T cells (Tregs) are altered in CVID patients. The expression of FOXP3 protein and also levels of inhibitory cytokines such as IL-10 are diminished in CVID [23]. The decrease of Treg cells is more pronounced in CVID patients with a severe decrease of switched memory B cells and expansion of CD21^{low} B cells [24].

As far as the innate immune system concerns, some reports have shown that dendritic cells present a severely altered differentiation, maturation, function, and reduced levels of co-stimulatory molecules that are critical for T cell activation [25]. Moreover, a peripheral decreased number of natural killer cells [26] and monocytes alterations directly correlating with T cell activation markers and with B cell imbalances have been reported in CVID [27].

3. CVID and infections

The typical symptoms of CVID are infections that may involve respiratory, gastrointestinal, and genitourinary tracts. Among these, the main clinical features are represented by upper and lower airway infections, which contribute substantially to the costs of care in these patients [28]. Approximately a half of CVID patients have at least one episode of pneumonia and the other half have recurrent bronchitis, sinusitis, and/or otitis.

Despite that immunoglobulin replacement therapy, which is the gold standard therapy of CVID, is effective in reducing the risk of infections, susceptibility to infections remains variable [29].

With regard to the causative pathogens of acute infection, bacterial infections are the most important and frequent, particularly those caused by *Streptococcus*, *Haemophilus*, *Moraxella catharralis*, *Neisseria meningitides*, and *Staphylococcus*. Viral infections, including *Rhinovirus*, *Herpes zoster*, and *Mycoplasma* spp. infections can be more frequent and more persistent in CVID. Pathogens that are considered opportunistic such as *Pneumocystis* and *Cytomegalovirus* are less frequent [30] but are commonly observed in CVID patients with low levels of CD4 + T cells.

When the lung infections are severe and occur repeatedly, two distinct patterns of chronic lung disease may develop: bronchiectasis and interstitial lung disease. Clinically, bronchiectasis is defined as permanent abnormal dilatation of the airway in conjunction with persistent or recurrent bronchial sepsis [31] and its prevalence in CVID varies greatly between centres. Bronchiectasis is more likely to affect older

age groups and is associated with a history of pneumonia and a CD4 + T cell count lower than 700 cells per μ l. By contrast, interstitial lung disease has been associated with increased CD4:CD8 T cell ratio, high IgM concentration, and a history of autoimmune haemolytic anaemia or immune thrombocytopenic purpura and tends to occur at younger age. The typical pattern of interstitial lung disease in CVID is a generalised diffuse reticular change, often with ground glass appearance at lower lobes [32].

4. CVID and inflammation

Dysregulation of immune system and recurrent infections lead to lymphoproliferation and inflammatory diseases. From 8 to 20% of patients with CVID develop granulomatous inflammation. Virtually, any organ can be involved, but the lung is a common site. Granulomatous disease is frequently associated with interstitial lung disease and with lymphocytic interstitial pneumonitis and follicular bronchiolitis [1,33]. An association between human *Herpesvirus* type 8 infections and the development of granulomatous and/or interstitial lung disease has been proposed in a small group of CVID patients [34], but further studies are required to better understand this association.

About half of patients with CVID has chronic diarrhoea with malabsorption and has histological findings suggestive of inflammatory bowel disease. The most common abnormality is nodular lymphoid hyperplasia, though there may be significant lymphoid infiltration in the intestinal lamina propria [1]. Unlike inflammatory bowel disease, lamina propria lymphocytes from CVID patients are skewed toward the production of Th1 pro-inflammatory cytokines such as IL-12 and INF- γ [35]. The small bowel often presents as a celiac-like enteropathy characterised by lymphocytic intraepithelial infiltration, shortness of villi, and hyperplastic crypts. Celiac-specific antibodies are usually absent, and histological abnormalities are nonresponsive to gluten-free diet [36].

Also, the liver may be involved in CVID. Hepatitis without evidence of viral infection has been reported with increased blood levels of alkaline phosphatase. Often, liver biopsy shows mild to moderate periportal lymphocytes infiltration and cholestasis. Moreover, nodular regenerative hyperplasia of the liver is present in more than 80% of CVID patients, who undergo liver biopsy [37].

5. CVID and autoimmune disease

The association between CVID and autoimmune diseases is well recognised, since autoimmune diseases occur in approximately 20–30% of patients with CVID. The coexistence of immunodeficiency and autoimmunity appears paradoxical; while antibody production in response to pathogens and vaccines is severely impaired or even lacking, the generation of autoantibodies might, at the same time, be excessive. Moreover, autoreactive B and T cells can be detected in patients with CVID, even if specific response to antigens is impaired [37,38]. On the other hand, considering that both innate and adaptive immune response abnormalities occur in CVID, such as expansion of abnormal B cell clones with altered trafficking and effector functions, altered cytokine expression and signalling, it is easier to understand the mechanisms that lead to a breakdown of self-tolerance in CVID.

The most common autoimmune disease found in CVID patients is immune thrombocytopenia (ITP) and autoimmune cytopenia. These complications are frequently associated with splenomegaly; however, hypersplenism is unable to completely explain this association and the pathophysiological link remains unclear [39]. It is important to underline that in more than 60% of CVID patients, the diagnosis of cytopenia may precede by many years the detection of hypogammaglobulinemia [40,41].

Other rheumatologic diseases, including polyarticular arthritis, like rheumatoid arthritis, occur in 10–30% of patients with CVID. This polyarthritis is distinct from rheumatoid arthritis because it is typically

seronegative and nonerosive. Classic rheumatoid arthritis occurs less frequently.

A wide spectrum of additional systemic and organ-specific autoimmune diseases, including systemic lupus erythematosus, pernicious anaemia, antiphospholipid syndrome, multiple sclerosis, Sjögren syndrome, psoriasis, thyroiditis, uveitis, vasculitis, and primary biliary cirrhosis has also been reported in CVID [37,38,42].

6. CVID, a crossroad between infection, inflammation, and autoimmunity

The understanding of the relationship among infections, autoimmunity, and inflammation is an interesting challenge for researchers. From this point of view, primary immunodeficiencies could help us to better understand the link between infections and autoimmunity.

The granulomas in CVID are sarcoid-like lesions. For this reason, some authors suggested that granulomatous disease in CVID is an atypical presentation of sarcoidosis on the genetic background of immunodeficiency. On the other hand, the immunodeficiency can lead to a dysregulated immune response to an unknown infectious agent, resulting in a diffuse granulomatous reaction [33], suggesting the likelihood of an infection as the original trigger. We have mentioned above the association between *Human Herpesvirus type 8* infection and granulomatous disease; moreover, a case of CVID with granulomatous and lymphoproliferative disease following an acute *Toxoplasma gondii* infection has been reported [43]. However, a systematic association of granulomatous lesion in CVID with particular infections has never been reported. Overall, the pathogenesis of both sarcoidosis and granulomatous lesion in CVID are not well understood; therefore, the relationship among immunodeficiency, infection, and granuloma formation remains elusive.

Recent studies have reported the involvement of human cytomegalovirus (HCMV) infection in the pathogenesis of chronic inflammation in CVID. The prevalence of HCMV infection ranges between 40 and 95% in the general population, depending on ethnic and socioeconomic conditions. Usually, infection in immunocompetent individuals proceeds without clinical manifestations. In immunocompromised patients, such as CVID patients, after the primary infection, virus can persist in the host and interfere with innate and adaptive immunity, with a pro-inflammatory effect [44]. Despite some alterations in T cell phenotype and function, CVID patients have a strong CD8 + T cell response to HCMV. Patients with evidence of HCMV exposure show a higher prevalence of inflammatory disease compared with non-exposed subjects. Furthermore, HCMV-specific CD8 + T cells are elevated in patients with CVID and inflammatory disease. Taken together, these findings strengthen the hypothesis that the combination between HCMV replication and excessive HCMV-specific CD8 + T cell response leads to inflammatory disease [45]. On the other hand, HCMV infection may be involved in the pathogenesis of some autoimmune diseases, such as systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and vasculitides, by molecular mimicry and bystander activation. Beside HCMV infection, many viruses, such as *Epstein Barr Virus*, and other infectious agents, such as *Salmonella* spp., *Staphylococcus aureus*, *Streptococcus pyogenes*, *Mycoplasma* spp., *Giardia lamblia*, may trigger an autoimmune response and eventually an autoimmune disease and all these pathogens are a frequent cause of infections in CVID patients.

If we consider together the immune abnormalities, the recurrent infections, and the chronic inflammation, it is easier to understand why autoimmunity and immunodeficiency can coexist.

7. CD21^{low} B cells, an elusive B cells population

Complement receptor type 2 (CD21) is expressed on B cells [46], follicular dendritic cells, thymocytes, and on a subset of peripheral T cells [47]. CD21 binds complement fragments C3d, C3dg, and iC3b that are

covalently bound to target antigens. Also, CD21 binds the low-affinity Fc-receptor for IgE and INF- α [48]. On B cells, CD21 forms a complex together with CD19 and CD81, which functions as a co-receptor for BCR. After stimulation of CD21 and BCR, the threshold of B cells activation is reduced. Therefore, CD21 functions as a bridge between the co-receptor complex and the BCR [49].

The surface expression of CD21 on B cells depends on the maturation stage of the cells. The majority of circulating B lymphocytes, including naive and memory B cells, express CD21, whereas plasmablasts and plasma cells lack or express low levels of CD21 [48].

Little is known about CD21^{low} B cells. Probably this cell subset develops from memory B-lymphocytes, because most of these cells are switched and their BCRs contain SHM. Moreover they express surface activation markers, such as CD69, CD80, and CD86, and have high levels of mRNA encoding the homing chemokine receptors CCR1, CCR5, CCR6. In vitro CD21^{low} B cells show poor proliferative capacity upon BCR stimulation; however, they respond to a combination of IL-2, IL-10, and CD40L. The expansion of CD21^{low} B cells clone is observed in some chronic infections, including HIV, hepatitis C virus, CMV, and *Plasmodium* spp. infection. In all these conditions, the increase of CD21^{low} B cells population is related to the duration of infection and to viremia. A B cells population with characteristics similar to CD21^{low} B cells is described in tonsils, where B lymphocytes are constantly exposed to foreign antigens. Taken together, these data suggest that CD21^{low} B cells derive from memory B cells or plasma cells after chronic stimulation.

CD21^{low} B cells have been described also in some autoimmune disease, such as systemic lupus erythematosus, Sjögren syndrome, and rheumatoid arthritis [48]. Moreover, the frequency of CD21^{low} B cells is increased in CVID patients and correlate with splenomegaly and autoimmunity [50].

Although CD21^{low} B cells have been studied in several diseases, little is known about their functions and data from the literature are contradictory [51,52]. CD21^{low} B cells appear to be in an activated state but at the same time express several inhibitory receptors. They do not proliferate in response to BCR triggering and are also prone to undergo apoptosis faster than CD21 + B cells do, suggesting a shorter half-life. However, these cells are able to respond to other stimuli and interact with other cells such as T lymphocytes subsets and/or innate immune cells, either through cell–cell contact or in response to cytokines. Moreover, CD21^{low} B cells may be enriched in autoreactive clones [52].

According with other studies [50], we have previously observed that CD21^{low} B cells are increased in CVID patients.

We therefore wanted to evaluate the levels of CD21^{low} B cells in patients with CVID and autoimmune thrombocytopenia, the most common autoimmune manifestation in CVID patients to better clarify the role of this specific B cell subset in a situation characterized by immunodeficiency, recurrent infections, and autoimmunity.

8. Materials and methods

8.1. Patients

We studied a cohort of 10 patients (2 males and 8 females, mean age 44.8 \pm 12 years) affected by CVID and autoimmune thrombocytopenia, attending the Unit of Clinical Immunology at the University Hospital of Verona. We also enrolled 10 patients with idiopathic autoimmune thrombocytopenia, 10 patients with CVID without autoimmune diseases, and 10 healthy controls. All patients with CVID fulfilled the ESID/PAGID criteria for the diagnosis of the disease. At enrolment, none of the patients had active infection or was affected by malignancies. Moreover, none was treated with antineoplastic or immunosuppressive drugs. All the patients affected by CVID were treated with regular monthly infusion of immunoglobulins at the dose of 0.4 g/kg.

8.2. FACS analysis

Blood was collected in tubes containing citrate. One hundred μL of whole blood was transferred in a 5 mL tube, lysed with ipertonic solution to deplete red cells, and washed with PBS at 1200 rpm for 5 min. Cells were then incubated with PE anti-CD21 and APC anti-CD19 monoclonal antibodies (Becton Dickinson, San Jose, CA, USA) for 30 min at 4 °C in the darkroom. Cells were washed again with PBS, and 100 μL of Perfect-count Microspheres (Cytognos, Salamanca, E) were added in order to calculate absolute cell number. Samples were finally acquired on a FACSCanto II cytometer (Becton Dickinson) and data analysed by FlowJo 9.7.6 software (Tree Star, Ashland, OR, USA).

8.3. Statistical analysis

The significance of differences was assessed by Student's t-test and was performed using GraphPad Prism version 5 (GraphPad Software Inc., La Jolla, CA, USA). A difference between groups with a $p < 0.05$ was considered statistically significant.

9. Results

9.1. CD21^{low} population.

We observed a statistically significant increase in CD21^{low} population percentage in the three pathological groups if compared with that of the healthy donors. Moreover, we found statistical differences between the two groups of patient affected by CVID, with patients affected also by autoimmune thrombocytopenia displaying a higher percentage of CD21^{low} population.

No significant differences were observed between patients affected by CVID and those affected by autoimmune thrombocytopenia and also between the two groups of patients affected by autoimmune thrombocytopenia (Fig. 2).

10. Discussion

CD21^{low} B cells possibly develop from memory B cells that have undergone chronic stimulation. In CVID patients, the chronic stimulation is due to recurrent infections; therefore, it is not surprising why there is an expansion of CD21^{low} B cells in this disease. An increased number of CD21^{low} B cells is observed in some autoimmune diseases, such as Sjögren's syndrome and systemic lupus eritematosus, even if the role of CD21^{low} B cells in the development of autoimmunity is still unclear. The data available so far suggest that CD21^{low} characterises a particular B cells subset that may represent a link between infection and autoimmunity.

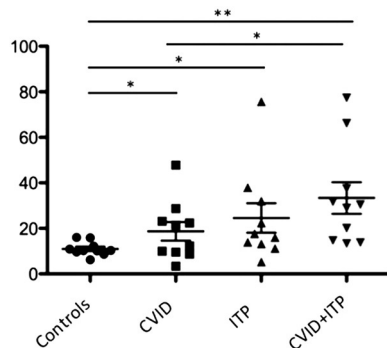


Fig. 2. Evaluation of CD21^{low} B cells percentage in the four groups analysed. Differences were found between controls and CVID patients ($p = 0.05$); controls and ITP patients ($p = 0.034$); CVID and CVID + ITP patients ($p = 0.046$); controls and CVID + ITP patients ($p = 0.006$).

Our data suggest that CD21^{low} cells are related to autoimmune clinical manifestations but do not clarify whether they play a role in favouring autoimmunity or whether they are an epiphenomenon. The profound immune dysregulation and the recurrent stimulation of immune system due to recurrent infections in CVID patients may cause expansion of B cells subsets with autoimmune features or allow them to escape normal regulatory controls, which are able to eliminate the autoimmune clones. Conflicting data are reported in literature: one hypothesis suggests that CD21^{low} cell population is characterised by autoreactive clone subsets [52], while another one considers CD21^{low} cells as anergic and prone to apoptosis [53]. Our aim is to clarify this discrepancy by sorting CD21^{low} cells and evaluate their ability to produce (auto)antibodies upon appropriate stimuli.

Take-home messages

- The association between CVID and autoimmune diseases is well known, since autoimmune diseases occur approximately in 20–30% of patients affected by CVID.
- The most common autoimmune diseases found in CVID patients are autoimmune thrombocytopenia and autoimmune cytopenia, but rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, and primary biliary cirrhosis have also been reported.
- In the presence of autoimmune thrombocytopenia or other systemic autoimmune or chronic inflammatory diseases, screening for hypogammaglobulinemia is strongly recommended.
- Conversely, screening for autoimmune and chronic inflammatory diseases is recommended in patients with CVID.
- B and T cells abnormalities may contribute to development of autoimmunity in CVID patients.
- CD21^{low} B cells are related with autoimmune manifestation and may represent a junction ring between infection and autoimmunity.

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