Human primary antibody deficiencies have been subgrouped in agammaglobulinemia, common variable immunodeficiency (CVID), class switch recombination (CSR) deficiencies, IgG subclass deficiencies, specific antibody deficiencies and other forms of hypogammaglobulinemia. While agammaglobulinemia is characterized by the severe reduction or even absence of B cells, other forms of hypogammaglobulinemia present with different patterns of peripheral B cell homeostasis. In CVID these patterns have been used by several groups to classify this heterogeneous disorder (1-4). These proposals were established in adult cohorts and pediatric cohorts probably need a separate evaluation due to the changing normal ranges during the first 12 years of life (5). Therefore the following thoughts are focusing on the adult cohort.

1) What are B cell patterns in CVID?
Circulating B cells can be dissected into 9 different populations according to their surface phenotype when staining for CD19 as a pan B-cell marker, the immunoglobulin isotypes IgM, IgA, IgG, (CD10), CD21, CD27 and CD38. The earliest step of B-cell differentiation seen in the periphery are transitional (T(t)) CD19+IgMhiIgDhiCD27−CD10+CD21−CD38++ B cells. These usually develop into mature follicular naïve CD19+IgM+IgD−CD27+CD10−CD21+CD38+B cells.

The memory compartment consists of CD19+IgMhiIgD−CD27+CD10−CD21+CD38− natural memory or so called Marginal Zone (MZ)-like B cells, classical IgG* or IgA* switched memory CD19+IgM−IgD−CD27+CD10−CD21−CD38−/− B cells, atypical IgG* or IgA* switched memory CD19+IgM−IgD−CD27+CD10−CD21+CD38−/− B cells, IgM* or IgG* or IgA* CD19+IgM+IgD−CD27+CD10−CD21−CD38++ plasmablasts and a circulating exhausted CD21low CD19hiIgM+IgD−CD27+CD10−CD21−CD38+B cell population (6, 7). Other markers have been suggested but don’t show a better separation of B cell populations in our hands.

Analysis of peripheral B cell patterns have demonstrated patients with low total B cell numbers with and without a block of differentiation at the transitional stage, patients with low or normal total B cell numbers with a block at different stages during memory development,
patients with an expansion of exhausted CD21\textsuperscript{low} B cells and patients with fairly normal pattern of circulating B cells.

2) Why B-cell phenotyping of CVID patients from a clinical point of view?
The number of CD19\textsuperscript{+} B cells needs to be determined in patients with very low immunoglobulins in order to exclude agammaglobulinemia. The phenotyping of B cells however is not required for the diagnosis of CVID. While most CVID patients present with a reduced number of class switched (cs) memory CD27\textsuperscript{+}IgD\textsuperscript{-}IgM\textsuperscript{-}B cells the current definition according to ESID/PAGID criteria (8) does not take into account whether patients are able to develop normal B cell memory or not. Most of the phenotyping has been done to identify subgroups of CVID patients. This originally was intended to separate patients on the basis of developmental blocks indicating different pathogenesis (see below). Interestingly, all classifications have demonstrated also a clinical relevance of B cell patterns. Thus the original publications (1-4), as well as several subsequent studies (9-13) demonstrated associations of certain subgroups with higher incidence of secondary manifestations like autoimmune cytopenias, granulomatous disease, splenomegaly and enteropathy. Thus the severe reduction of cs memory B cells was associated with any of these secondary manifestations. Similarly, patients with expanded CD21\textsuperscript{low} B cells present more often with splenomegaly, autoimmune cytopenias or/and granulomatous disease. One group associated lack of natural IgM\textsuperscript{+} memory B cells with bronchiectasis (14).

Two reports suggest that the presence of cs memory B cells correlates with a better residual vaccination response in CVID (12, 15) which might be useful in guiding which patients might profit from vaccination. It currently remains open whether B cell phenotypes permit differential diagnosis between transient hypogammaglobulinemia and CVID in children. According to current definitions about 25\% of CVID patients present with (near) normal numbers of cs memory B cells.

3) What can B cell patterns tell us about the pathophysiology of CVID?
B cell phenotyping was originally set up to determine subgroups with distinct pathophysiology. While this has been successful to some extent, it has not become the full success story for different reasons. CVID still remains very complex even after breaking up into different subgroups. While specific markers are helpful in predicting certain monogenetic forms of CVID, even the same defect can present in different subgroups according to B cell phenotype demonstrating epigenetic factors influencing B cell presentation beyond the genetic impact. What did we learn so far?
a) Correlation of monogenetic defects and B cell patterns

Several of the monogenetic defects will already be suspected due to the abnormal presentation of the B cell phenotype. Thus CD19 deficiency (16), CD81 deficiency (17), CD21 deficiency (18) are all discovered by the lack of respective staining. CD27 deficiency (19, 20) even though not CVID can be a differential diagnosis which might be suspected when CD27 staining is missing on B and T cells. ICOS deficiency is always associated with a lack of cs memory B cells (21, 22) due to its strong effect on germinal center development. Similarly, CD19 and CD81 deficiency are associated with reduced cs memory B cells. BAFF-R deficiency (23) is associated with a block of early B cell differentiation at the TI stage reducing total, naive and memory B cell number while TI B cells are relative expanded compatible with the important role of the B cell survival factor at this early peripheral developmental stage. TACI deficiency associated with CVID (24, 25) does not imprint on circulating B cells. Patients with TACI mutations can present with very different alterations of B cell differentiation suggesting that TACI itself does not play a major role in the homeostasis of circulating B cells and may rather impact plasma cell differentiation and maintenance.

b) Correlation of B cell patterns with functional defects

B cell patterns have been associated with BCR signaling especially Ca2+ response (26, 27) as well as with proliferation history somatic hypermutation (4). Thus two groups identified a CA2+ signaling defect in patients with CVID patients with expanded CD21low B cells (Freiburg Ia or EUROClass CD21lo). It is still unknown what the cause of the decreased BCR response is. In an extensive study Driessen et al correlated proliferation history by KREC analysis and somatic hypermutation to dissect immunological phenotypes in CVID. Thus they found a group of with increased homeostatic proliferation of naïve B cells with poor BM output and poor germinal center response possibly due to a DNA repair defect. A second group is characterized by the relative expansion of transitional B cells due to a block at this stage and reduction of the subsequent populations. BAFF-R deficiency would be a prototype of this group. The third group of patients is described by the reduction of natural and cs memory B cells supposedly due to an activation defect, but this remains to be determined. CD19 and CD81 deficiency would fall into this group. In the fourth group only post Germinal center cs memory B cells were reduced and in the final group B cell pattern was fairly normal and therefore a defect in terminal plasma cell production was postulated.

While this analysis is too laborious for diagnostic purposes it has revealed some additional aspects fo the disturbed B cell differentiation in CVID patients.

c) B cell patterns beyond CVID

None of the B cell patterns are CVID specific. Thus an expansion of TI B cells can be found in patients with leaky agammaglobulinemia, with X linked lymphoproliferative disease (XLP),
combined immunodeficiency in CARD11 deficiency and idiopathic low CD4 syndrome. A loss of cs memory B cells is associated with many primary immunodeficiency disorders like FAS-ALPS, CSR deficiency, (S)CID, Wiskott Aldrich syndrome, STAT3 deficiency and others.

Conclusion:
While B cell patterns are helpful in differentiating subgroups hunting for the pathogenesis of the different forms of CVID and their usefulness in clinical application is suggested by the association studies available so far, prospective studies have to be performed in order to determine whether these patterns also carry predictive values. Clinical trials in CVID should always include immunological phenotyping in order to improve interpretation of the results.

References


