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Is the humoral immunity dispensable for the pathogenesis of psoriasis?

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Abstract:

Background: Imbalances of T cell subsets are hallmarks of disease-specific inflammation in psoriasis. However, the relevance of B cells for psoriasis remains poorly investigated.

Objective: To analyse the role of B cells and immunoglobulins for the disease specific immunology of psoriasis.

Methods: We characterized B cell subsets and immunoglobulin levels in untreated psoriasis patients (n=37) and compared them to healthy controls (n=20) as well as to psoriasis patients under disease-controlling systemic treatment (n=28). B cell subsets were analyzed following the flow cytometric gating strategy based on the surface markers CD24, CD38 and CD138. Moreover, immunofluorescence stainings were used to detect IgA in psoriatic skin.

Results: We found significantly increased levels of IgA in the serum of treatment-naïve psoriasis patients correlating with disease score. However, IgA was only observed in dermal vessels of skin sections. Concerning B cell subsets, we only found a moderately positive correlation of $CD138^+$ plasma cells with IgA levels and disease score in treatment-naïve psoriasis patients. Confirming our hypothesis that psoriasis can develop in the absence of functional humoral immunity, we investigated a patient who suffered concomitantly from both psoriasis and a hereditary common variable immune defect (CVID) characterized by a lack of B cells and immunoglobulins. We detected variants in three of the 13 described genes of CVID and a so far undescribed variant in the ligand of the TNFRSF13B receptor leading to disturbed B cell maturation and antibody production. However, this patient showed typical

psoriasis regarding clinical presentation, histology or T cell infiltrate. Finally, in a group of psoriasis patients under systemic treatment, neither did IgA levels drop nor did plasma cells correlate with IgA levels and disease score.

Conclusion: B cell alterations might rather be an epiphenomenal finding in psoriasis with a clear dominance of T cells over shifts in B cell subsets.

Introduction

Psoriasis is a highly prevalent chronic inflammatory skin disease which is associated with metabolic and cardiovascular co-morbidities [1-3]. In the pathogenesis of psoriasis, T lymphocytes, in particular Th1 and Th17 cells [4], and their cytokines have been identified as key cellular players leading to a broad set of effective and specific therapies [5, 6]. However, increasing evidence from other Th17 mediated diseases such as multiple sclerosis and rheumatoid arthritis suggest that B cells might be equally important players [7]. In line with this, clinical trials demonstrated that B cell depleting therapies reduced relapses and disease activity in patients suffering from multiple sclerosis and improved disease symptoms in patients with rheumatoid arthritis [7-10].

As precursors of differentiated plasma cells, B lymphocytes not only produce antibodies, but also play an important immunological role as antigen-presenting cells and producers of a broad array of cytokines, which control early and established T cell-mediated responses [11].

In psoriasis, B cells were indeed detected in lesional skin [12, 13] and altered frequencies of circulating B lymphocytes in psoriasis have been described [14]. However, it is still unclear whether B cells have a functional role in the disease specific immunology of psoriasis or if

alterations only occur as a bystander phenomenon. In-depth data – in particular comprehensive characterization of different B cell phenotypes in the context of their developmental stage - are sparse. Recently, the subset of $CD19^{+}CD24^{hi}CD38^{hi}$ B cells has been shown to maintain regulatory T cells while limiting Th1 and Th17 differentiation [15], which may imply significant impact in the context of the psoriatic inflammation.

In this study, B cell subtypes and immunoglobulins were analyzed in peripheral blood in a large cohort of psoriasis patients and compared to healthy controls. Our findings were tested for correlation to disease activity (PASI) and validated by immunofluorescence stainings. Furthermore, to estimate the significance of B cells in psoriatic inflammation in vivo, a patient suffering from psoriasis as well as a B cell immunodeficiency was investigated intensively. Finally, B cell subsets were compared between the group of therapy-naïve and systemically treated psoriasis patients to detect whether disease control is dependent on B cell alterations.

Material and Methods

Patients

Thirty-seven treatment-naive patients with psoriasis and Psoriasis Area and Severity Index [PASI] score > 5 (42.0 ± 2.4 years; PASI: range 6.2 to 42.3, mean 14.9), and 20 healthy volunteers (48.2 ± 3.2 years) were enrolled in this study. No age (p=0.15, one-way ANOVA) or sex (p=0.38, χ^2 test) disparities were observed between the groups. To define if successful systemic treatment would affect B cell and immunoglobulin status, a second cohort of 28 patients with psoriasis under systemic treatment with PASI < 5 (52.1 ± 2.1 years; PASI: range 0.0 to 4.7, mean 1.7) was established. Among these patients, eight patients were treated with anti-TNF-α medication, eight patients with methotrexate, five patients with anti-IL-

23/IL-12 medication, three patients with fumaric acid esters, three patients with PDE-4 inhibitor and one patient with acitretin. Severity scores were obtained using the PASI system. All patients and control subjects gave their written consent to participate in the study, and the study was approved by the local ethical committee (project number 44/16S).

Whole blood cell surface staining

Whole peripheral blood was lysed using red blood cell lysis buffer containing NH_4Cl, $KHCO_3$ and EDTA dissolved in H_2O. After blocking unspecific antibody binding with Human BD Fc Block (Becton, Dickinson and Company, Franklin Lakes, New Jersey) peripheral blood cells were stained using fluorochrome-labeled antibodies binding to cell-surface markers (anti-CD19, anti-CD24, anti-CD38, anti-CD138, , anti-CD3,; all BD; anti-CD138: R&D Systems, Minneapolis, Minnesota; anti-CD20, anti-IgA: Miltenyi Biotec, Bergisch Gladbach, Germany). Dead cells were detected and excluded from analysis by LIVE DEAD^{TM} Fixable Aqua Dead Cell Stain Kit: Thermo Fisher Scientific, Waltham, Massachusetts).

Flow cytometric analysis and nomenclature

The $CD19^+$ B cells were grouped in five subsets according to their CD24 and CD38 expression, two markers that are expressed on all B cells but differentially regulated during B cell development [16]. This well-established approach enables to distinguish $CD24^+CD38^-$ primarily memory B cells, $CD24^{int}CD38^{int}$ mature naïve B cells, $CD24^{hi}CD38^{hi}$ transitional/regulatory B cells, $CD24^-CD38^+$ plasmablasts/plasma cells and $CD24^-CD38^-$ new

memory B cells [17-19]. Furthermore, we analyzed CD138 expression in order to gain deeper insight into the plasma cell compartment.

Cells stained with fluorochrome conjugated antibodies against corresponding surface antigens were acquired with a LSRFortessa flow cytometer (BD) and analysed using FlowJo Software, Version 10 (FlowJo, LLC, Ashland, Oregon).

Statistical analysis

Statistical analysis was performed using GraphPad Prism 7.00 Software (GraphPad Software, La Jolla, California). Mann-Whitney U test was used to compare between variables. Variables were correlated by using Spearman rank correlation. All values are expressed as means with standard error of the mean (SEM).

Ethics

All methods were carried out in accordance with relevant guidelines and regulations. Human patient procedures were approved by the Ethics Committee of the Technical University of Munich (project number 44/16S) and all patients and control subjects provided informed consent.

Results

IgA serum levels are elevated in psoriasis and correlate with disease severity

In untreated patients with psoriasis, as well as in our cohort of control subjects, we first analyzed humoral serum proteins, namely IgM, IgA, IgG, IgE and complement factors C3

and C4. We found that C3 and C4 concentrations were higher in the serum of psoriasis patients (125 ± 4.6 mg/dl for C3; 26.2 ± 1.2 mg/dl for C4) than in healthy controls (105.7 ± 3.3 mg/dl for C3, p=0.0034; 21.4 ± 1.3 mg/dl for C4, p=0.0096, Supplementary Figure S1 A and B). Concerning immunoglobulins, we found no differences of the serum levels of IgG and IgM between the cohorts (Supplementary Figure S1 C and D). IgE levels were significantly increased in psoriasis (256.8 ± 62.2 IU/ml) compared to healthy controls (78.39 ± 24.61 IU/ml, p=0.0146) (Supplementary Figure S1 E). Most significantly, however, we found IgA levels higher in psoriasis (269.2 ± 20.6 mg/dl) than in healthy controls (160.54 ± 17.63 mg/dl, p<0.0001, Figure 1 A). More importantly, IgA serum levels but not IgE levels in the serum of psoriasis patients showed a correlation with PASI (r=0.43, p=0.013 for IgA, r=0.23, p=0.21 for IgE; Figure 1 B, Supplementary Figure S1 F). Accordingly, IgA could also be detected in psoriatic skin. However, in all sections (n=18) examined, IgA was only found in dermal vessels of lesional psoriatic skin and not in epidermal or dermal tissue (Figure 1C).

Characterization of B cell subsets does not reveal profound psoriasis specific aberrations

Further investigating the discrepancy of elevated IgA in serum of psoriasis patients but absent accumulation in psoriatic skin, we analyzed B cells as sources of IgA in both psoriatic skin and blood. In line with our findings for IgA in the skin, immunofluorescent double stainings of both CD19 and CD8 (marker for cytotoxic T cells) revealed only few B cells as compared to the abundance of T cells in psoriatic skin (Supplementary Figure S4). To clarify if elevated IgA serum levels are paralleled by an altered composition of B cell subsets in the peripheral

blood, we next analyzed the distinct B cell subsets using the common gating strategy based on CD24 and CD38[17, 18]. Within the five different subsets in the CD24/CD38 gates, no significant differences between the two groups of untreated psoriasis patients and control subjects were found for the $CD19^{+}CD38^{-}CD24^{-}$ new memory B cells (Psoriasis: 2.2 ± 0.2%, control subjects: 2.1 ± 0.3, p=0.7662), $CD19^{+}CD38^{hi}CD24^{hi}$ transitional regulatory B cells (Psoriasis: 4.2 ± 0.4%, control subjects: 5.05 ± 0.7%, p=0.7781), $CD19^{+}CD38^{-}CD24^{hi}$ primarily memory B cells (Psoriasis: 27 ± 2.6%, control subjects: 24.4 ± 2.8%, p=0.8316) and mature B cells, as defined by $CD19^{+}CD38^{int}CD24^{int}$ (Psoriasis: 59.9 ± 2.7%, control subjects: 62.6 ± 2.8%, p=0.8386). Regarding the population of $CD19^{+}CD24^{-}CD38^{+}$ plasmablasts a trend for a higher proportion was observed in psoriasis (2 ± 0.4%) as compared to control subjects (1.4 ± 0.3%, p=0.2561, Figure 2 A).

A substantial proportion of the cells within the fraction of $CD19^{+}CD24^{-}CD38^{+}$ plasmablasts in the blood was previously described to express CD138, a proteglycan that is a hallmark of plasma cells [20]. Moreover, as steady-state circulating $CD38^{hi}CD138^{+}$plasma cells are known to secrete IgA [20] and IgA was elevated in our cohort of psoriasis patients as compared to healthy controls, we next focused on the fraction of $CD19^{+}CD24^{-}CD38^{+}CD138^{+}$ plasma cells within the population of $CD19^{+}CD24^{-}CD38^{+}$ plasmablasts. Although similar frequencies of this cell population were detected in psoriasis (12.5 ± 1.18%) and healthy volunteers (12.6 ± 1.5, p=0.9411 Figure 2 B) we found only in psoriasis but not in healthy controls a moderate correlation between IgA levels and the $CD19^{+}CD24^{-}CD38^{+}CD138^{+}$ subset (r=0.4, p=0.02 for psoriasis; r=-0.03, Figure 2 C; p=0.9 for healthy controls). Besides, PASI was positively correlated with the frequency of $CD19^{+}CD24^{-}CD38^{+}CD138^{+}$ plasma cells (r=0.39; p=0.02, Figure 2 D). Furthermore, we directly examined IgA expression on $CD19^{+}CD24^{-}CD38^{+}CD138^{+}$ plasma cells and found that $CD19^{+}CD24^{-}CD38^{+}CD138^{+}$ cells

are indeed IgA positive. Moreover, $CD19^{+}CD24^{-}CD38^{+}CD138^{+}IgA^{+}$ plasma cell frequencies also correlated with PASI (r=0.883, p=0.015, Supplementary figure S5 A and B).

Development of psoriasis in a patient suffering from common variable immune deficiency accompanied by a severe lack of B cells and immunoglobulins

To interpret our results for the relevance of disease pathogenesis in human psoriasis, we eventually had the chance to also analyse a patient (A.B.) who suffered from a hereditary common variable immunodeficiency characterized by a lack of B cells and immunoglobulins and – at the age of thirty – developed psoriasis for the first time. On admission, the patient displayed the full phenotype of psoriasis vulgaris both clinically (Figure 3 A) and histologically (Figure 3 B). The family history for psoriasis was positive and the PASI of A.B. on admission was 30. In respect of the findings from the cohort of psoriasis patients, this specific patient might offer the opportunity to clarify the question if B cells are of high relevance in the pathogenesis of psoriasis or – in contrary – if the lack of B cells had been irrelevant for the development of psoriasis. We first analysed the functionality of peripheral blood mononuclear cells (PBMC) and found that PBMC stimulated by α-CD3 and α-CD28, as well as by Phytohemagglutinin (PHA) and pertussis toxin showed substantial proliferation as assessed by H3-Thymidine incorporation indicating intact T cell function upon stimulation (Supplementary Figure S2 A). Next, we isolated T cells from lesional skin of the patient, stimulated them and compared their cytokine profile to a representative cohort of cytokine profiles from patients with psoriasis randomly picked from the untreated cohort (n=11). We found comparative values for A.B. and psoriasis patients with high amounts of TNF-α, IFN-γ and IL-17 indicating a Th17 profile that was not altered by a lack of B cells and their respective cytokines (Supplementary Figure S2 B).

To characterize the underlying immune defect of A.B. in more detail, we performed total RNA sequencing of lesional skin in this patient and analyzed genetic variants within these transcripts. In the transcripts of the 13 described CVID genes, we identified 6 synonymous and 1 nonsynonymous variants in three of them, namely NFKB1, NFKB2 and PRKCD. In addition, we identified 1 nonsynonymous variant in TNFSF13, the ligand of the TNFRSF13B receptor. This receptor also belongs to the 13 described genes of CVID and shows strong integration with the other CVID genes when depicting all CVID genes in a network (Figure 3 C).

We then analyzed peripheral B cell subsets from PBMCs and serum IgA in A.B. We measured a strong decrease of IgA levels in A.B. (57 mg/dl) as compared to psoriasis (269.2 $\pm$ 20.6 mg/dl) and healthy controls (160.54 $\pm$ 17.63 mg/dl, Figure 3 D). Besides, we found a marked reduction of peripheral $CD19^+$ B cells in A.B. (2.3 %) as compared to psoriasis with 11.1 ± 0.7 % and healthy controls with 9.4 ± 0.8 %, Figure 3 E).

In contrast to the above described cohort of patients with psoriasis and healthy controls, A.B. showed increased percentages of new memory $CD19^+CD38^-CD24^-$B cells (13.7 %), primarily memory $CD19^+CD38^-CD24^{hi}$ B cells (63.4 %) and $CD19^+CD38^{hi}CD24^-CD138^{hi}$ plasma cells (51.6 %), whereas the population of $CD19^+CD38^{int}CD24^{int}$ mature B cells (16%) and $CD19^+CD38^{hi}CD24^{hi}$ regulatory B cell was markedly decreased or almost absent (0.16 %).

B cell subsets in patients under disease-controlling systemic anti-psoriasis treatment regimens remain broadly unchanged

To further understand the relevance of B cells in the context of psoriasis, we analyzed IgA levels and above characterized B cell subsets in a group of psoriasis patients showing stable disease activity (PASI < 5 in all patients) under systemic treatment. For IgA levels, no

significant differences between the cohort of untreated patients (PASI > 5) and treated patients (PASI < 5) were detected (p=0.5148, Figure 4 A). Moreover, PASI did not correlate with IgA (Supplementary Figure S3 D) within the cohort of treated patients. Apart from significant reduced percentages of plasmablasts ($CD19^+CD24^-CD38^+$) within the group of treated patients as compared to the group of untreated patients (p=0.02, Figure 4 B), no differences between treated and untreated patients were observed within the remaining four subsets of new memory B cells, transitional regulatory B cells, primarily memory B cells and mature B cells (Figure 4 B). Also, when comparing $CD19^+CD24^-CD38^+CD138^+$ plasma cells between the two cohorts, we found no significant difference between treated and untreated patients (p=0.14, Supplementary Figure S3 A). Besides, the $CD19^+CD24^-CD38^+CD138^+$ plasma cells - for which we showed positive correlations with IgA and PASI in the untreated cohort (Figure 1 B) - did not correlate with IgA and PASI within the group of treated patients (Supplementary Figure S3 B and C).

Discussion

Psoriasis is understood as a T cell driven chronic inflammatory skin disease. In contrast to T cell research in the field of psoriasis, B cells as important counterparts of T cells in the adaptive immune system have not yet been investigated comprehensively. Several case reports described new-onset psoriasis during B cell depleting therapies [21-24]. Moreover, studies investigating B cell functions and phenotypes in psoriasis have revealed contradictory results. A study investigating natural killer cells and B cells in psoriasis found increased levels of B cells in psoriasis as compared to healthy controls [14], whereas Czarnowicki et al. found similar frequencies of B cells in psoriasis and healthy controls [18] – a finding which is in line with our results. While we did not detect differences in the frequency of

$CD19^{+}CD38^{hi}CD24^{hi}$ regulatory B cells one study showed increased frequencies [25] and another one even decreased frequencies of these regulatory B cells in psoriasis [18].

In our study, we found increased IgA levels in treatment-naïve patients with psoriasis in the serum corroborating the findings of earlier studies [26, 27]. Besides, we found correlation of IgA levels with $CD24^{-}CD38^{+}CD138^{+}$ plasma cells in our cohort of untreated patients. The relative distribution of this subset was not different between the cohort of psoriasis and healthy volunteers, however, we found a significant correlation of this subset in untreated patients with PASI. This indicates that these cells might exert a distinct specific role in the inflammatory processes of psoriasis. However, during disease controlling systemic treatment, neither did IgA levels and percentages of $CD19^{+}CD24^{-}CD38^{+}CD138^{+}$ plasma cells drop, nor did $CD138^{+}$ plasma cells correlate with PASI and IgA levels indicating a rather epiphenomenal than a disease influencing role of IgA and $CD19^{+}CD24^{-}CD38^{+}CD138^{+}$ plasma cells. Along with this, we only found IgA deposits in the dermal blood vessels, but not in the tissue as in dermatitis herpetiformis where it plays a clear pathophysiological role [28]. IgA in the dermal vessels of skin sections has been described for Henoch-Schönlein purpura [29] but also for apparently healthy skin of patients with primary IgA nephropathy, Henoch-Schönlein purpura, or alcoholic liver disease [30]. These diseases including psoriasis are characterized by generalized inflammation, leading to the assumption that IgA in blood vessels but not in the skin might be an epiphenomenal finding in the course of generalized inflammation.

Furthermore, we analyzed a patient (A.B.) suffering from psoriasis and B cell deficiency concomitantly, thus representing an ideal role model to investigate the significance of B cells as a proinflammatory player in the pathogenesis of psoriasis in humans. On the transcriptome level, we found six synonymous and one nonsynonymous variants in three of the 13 CVID

genes NFKB1, NFKB2 and PRKCD. Besides, we identified a nonsynonymous variant in TNFSF13, a ligand of the TNFRSF13B receptor. This receptor belongs to one of the 13 described CVD genes and has been shown to be involved in B cell function and – in its mutated form – to disrupt antibody production leading to immune dysfunction [31]. As shown by our network analysis, TNFSF13 and its receptor show strong integration with other factors of the CVID network. As expected by the genetic background, our patient presented with decreased B cell counts and IgA level, but high disease score, thus indicating that B cells and IgA deposits might be dispensable for the development of psoriasis. Since psoriasis patients did not show an overall decreased frequency of $CD24^{hi}CD38^{hi}$ regulatory B cells, a diminished protective B cell phentotype as a general mechanism in the pathogenesis of psoriasis can be excluded. However, a decreased protective role of e.g. regulatory B cells influencing the pathogenesis in a subset of patients cannot be excluded by our data.

As the functions of B cells are not limited to the production of antibodies, but also include activation of T cells, we also investigated T cell function in our patient A.B.. We showed, that T cells are fully functional in A.B. with a psoriasis typical Th17 phenotype.

In A.B, rather low frequencies of regulatory B cells were detected, a common finding in patients with common variable immunodeficiency [32]. As regulatory B cells have been shown to play an important role in the development of regulatory T cells and for controlling T cell activation and thus autoimmunity [32], one might argue that A.B. developed psoriasis due to due to limited regulatory B cell mediated control of T cell activity. However, in our cohort of psoriasis patients an overall decreased frequency of $CD24^{hi}CD38^{hi}$ regulatory B cells could not be detected strongly questioning a general mechanism of protective B cell phenotypes in the pathogenesis of psoriasis. Along with this, Yanaba et al. showed that in the murine imiquimod model skin inflammation was not less but in the contrary more severe in $CD19^{-/-}$ mice than in WT mice corroborating our point of CD19+ cells not primarily driving

psoriatic inflammation. Yet, they found that inflammatory responses were negatively regulated by a unique IL-10-producing $CD1d^{hi}CD5^{+}$ regulatory B cell subset [33] hinting at a decreased protective role of regulatory B cells in a subset of psoriasis patients, as e.g. in our patient A.B. However, in A.B., the positive family history of psoriasis but not CVID, challenges a crucial role ofB cells. Consistent with this genetic line of argumentation, microarray data, including ours, as well as big GWAS studies have mainly found aberrations in T cell and not B cell related pathways [34-36]. Not least our immunofluroscent stainings revealed that B cells are rarely found in psoriatic skin as compared to the dense infiltrate of T cells providing one reason why B cell depleting therapies have not proven resounding success for the therapy of psoriasis in contrast to the successful target oriented therapies that are focused on T cell mediated pathways [37].

Although we analyzed a broad set of surface markers used for in-depth phenotyping of B cells, we eventually found rather few differences between the B cell subtypes of psoriasis as compared to healthy volunteers. This hints at the conclusion that psoriasis can be elicited in the lack of B cells and immunoglobulins. Nevertheless, it might be possible, that relevant changes in B cell subsets are not detectable in the periphery, but in primary and secondary lymphoid organs such as bone marrow or lymph nodes, which were not accessible in our study. Although, reduced frequencies of regulatory and potential protective B cell subsets as a general pathomechanism for psoriasis could be excluded based on our data, they might be relevant for a subset of patients. Further functional studies beyond pure characterization of surface markers – even if as detailed as in our study – are necessary to reveal the disease-specific contribution of B cells and thus the therapeutic potential of targeting specific B cell subtypes.

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Figure legends

Fig.1: **IgA serum levels are elevated in psoriasis and correlate with disease severity.** IgA levels are significantly increased in psoriasis as compared to healthy controls (A). In psoriasis patients, IgA levels show a moderate correlation with disease score PASI (B). Representative immunofluorescence staining of psoriatic skin shows that IgA could also be detected in psoriatic skin (C). However, IgA was only found in dermal vessels of lesional psoriatic skin and not in epidermal or dermal tissue. Scale bar = 100 µm. Inset at 3x magnification.

Fig.2: Characterization of B cell subsets using the CD24/CD38 gating strategy. Within the five different subsets in the CD24/CD38 gates, no significant differences between the two groups of untreated psoriasis patients and control subjects were found for the $CD19^{+}CD38^{hi}CD24^{hi}$ transitional regulatory B cells (I), $CD19^{+}CD38^{int}CD24^{int}$ mature B cells (II), $CD19^{+}CD38^{-}CD24^{hi}$ primarily memory B cells (IV) and $CD19^{+}CD38^{-}CD24^{-}$ new memory B cells (V). Regarding the population of $CD19^{+}CD24^{-}CD38^{+}$ plasmablasts (III) a trend for a higher proportion was observed in psoriasis (A). Regarding the fraction of $CD19^{+}CD24^{-}CD38^{+}CD138^{+}$ plasma cells within the fraction of plasmablasts, similar frequencies were detected in psoriasis and healthy volunteers (B). But a moderate correlation between plasma cells with IgA levels (C) and PASI (D) was found.

Fig. 3: Index patient A.B. suffering concomitantly from psoriasis and a common variable immune deficiency (CVID). Patient A.B. displayed the full phenotype of psoriasis vulgaris with demarcated red scaly plaques all over the body (A). Histological examination showed characteristic epidermal thickening with regular elongation of rete ridges,

lymphocytic infiltration and neutrophilic micro-abscesses (B). RNA sequencing of lesional skin and analysis of genetic variants in A.B. revealed 6 synonymous and 1 nonsynonymous variants in three of the 13 described CVID genes, namely NFKB1, NFKB2 and PRKCD and 1 nonsynonymous variant in TNFSF13, the ligand of the TNFRSF13B receptor (C). In A.B. IgA levels are markedly reduced as compared to psoriasis and healthy controls (D). Also, B cell levels are decreased as compared to psoriasis and healthy controls (E). Moreover, A.B. showed increased percentages of new memory $CD19^{+}CD38^{-}CD24^{-}$B cells, primarily memory $CD19^{+}CD38^{-}CD24^{hi}$ B cells and $CD19^{+}CD38^{hi}CD24^{-}CD138^{hi}$ plasma cells, whereas the population of $CD19^{+}CD38^{int}CD24^{int}$ mature B cells and $CD19^{+}CD38^{hi}CD24^{hi}$ regulatory B cell was markedly decreased or almost absent (E).

Fig. 4: B cell subsets in patients under disease-controlling systemic anti-psoriasis treatment regimens remain broadly unchanged. For IgA levels, no significant differences between the cohort of untreated psoriasis patients (PASI > 5) and psoriasis patients under disease controlling systemic treatment (PASI < 5) were detected (A). Apart from significant reduced percentages of plasmablasts ($CD19^{+}CD24^{-}CD38^{+}$) within the group of treated patients as compared to the group of untreated patients (p=0.02, Figure 4 B), no differences between treated and untreated patients were observed within the remaining four subsets of new memory B cells, transitional regulatory B cells, primarily memory B cells and mature B cells (B).

Figure 1_Thomas and Küpper et al.

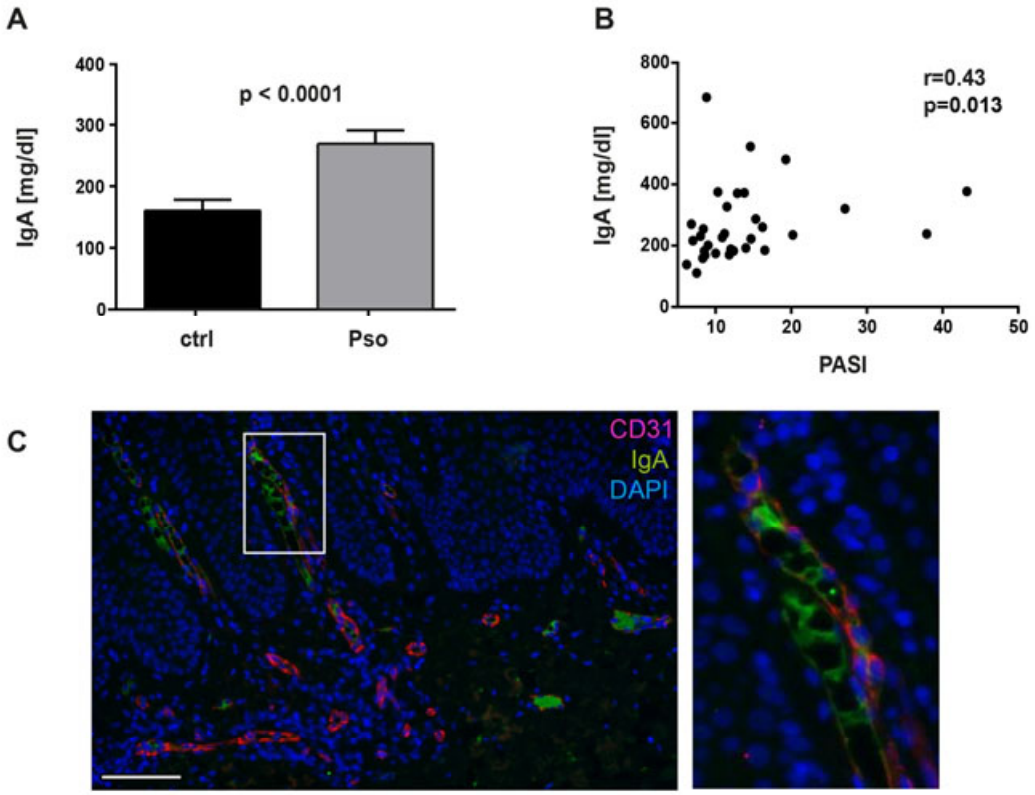

Figure 2_Thomas and Küpper et al.

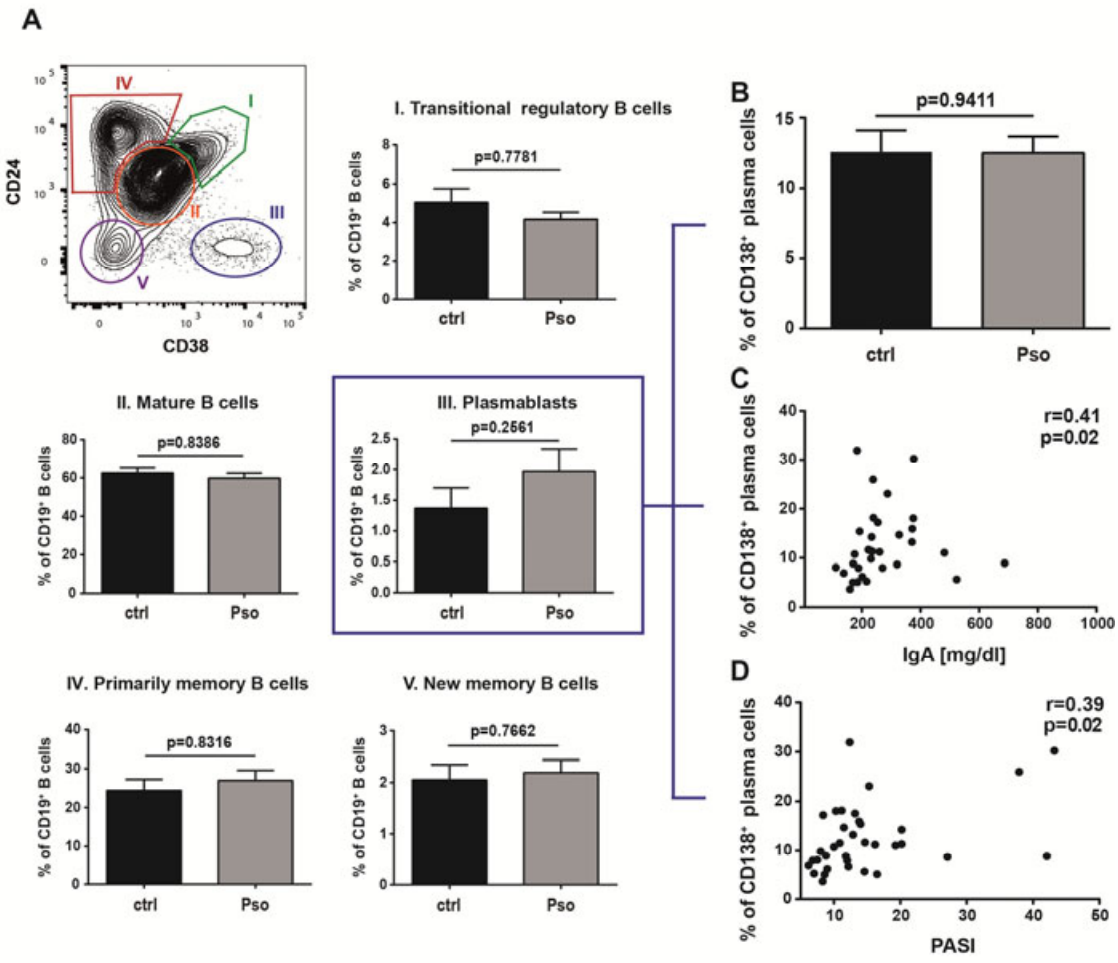

Figure 3_Thomas and Küpper et al.

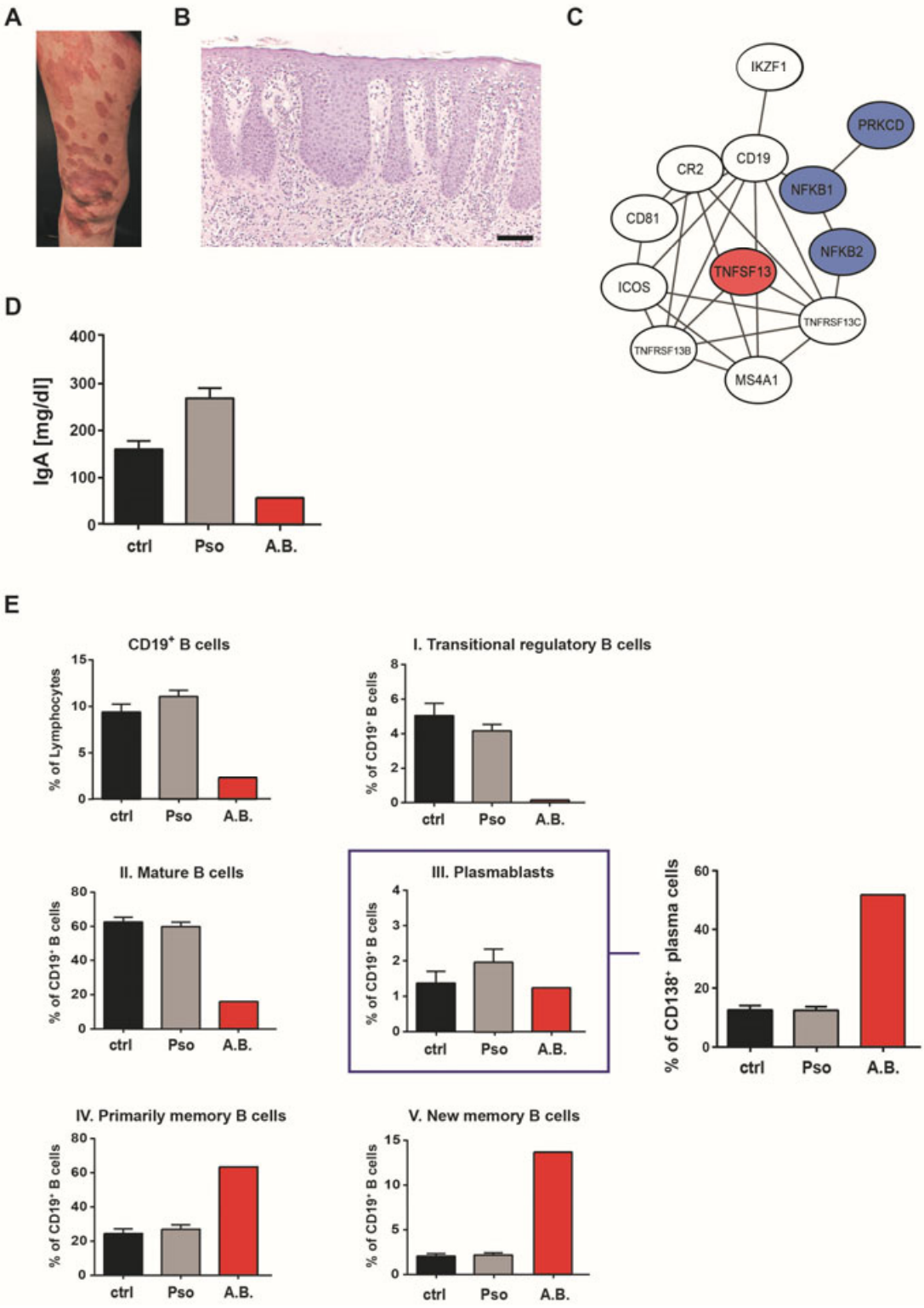

Figure 4_Thomas and Küpper et al.