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Review

Serum and blister fluid levels of cytokines and chemokines in pemphigus and bullous pemphigoid

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ABSTRACT

Bullous pemphigoid and pemphigus constitute two major autoimmune blistering diseases (AIBD) with complicated disease pathomechanisms involving a multitude of cytokines and immunological pathways. The purpose of our literature review of the cytokines and chemokines involved in these AIBDs was to allow for a meta-analysis of studies detailing differential cytokine and chemokine changes in these conditions. Elucidation of inflammatory pathways could lead to more targeted therapies, several of which specific monoclonal antibodies already exist and are used safely for other autoimmune diseases. A systematic review of the Pubmed/Medline database was performed for articles characterizing cytokines/chemokines involved in BP and pemphigus. Further, a meta-analysis was carried out using standardized methods, including assessment for heterogeneity. The results of our analysis demonstrated numerous inflammatory alterations in these AIBDs. Significant alterations included serum levels of IL-5, IL-6, IL-8, IL-17, CCL-17, and CCL-26 in patients with BP, and increased blister fluids levels of IL-5, IL-6, IL-8, CCL11, and TNF-α. Blister fluid levels of IL-1α are decreased in BP. In pemphigus, we identified significantly increased serum levels of IL-10, IL-17, and CCL17. We have additionally summarized all studies excluded from meta-analysis to provide a comprehensive summary of cytokine/chemokine alterations in these two conditions.

1. Introduction

Autoimmune blistering diseases (AIBD) encompass a large, heterogenous group of chronic diseases characterized by autoantibodies targeting the desmosome or the basement membrane zone (BMZ). Two of the most common of these include bullous pemphigoid (BP), and pemphigus, of which pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the most common subtypes. Although there is considerable histological and immunological overlap between the various subepidermal blistering diseases, pemphigoid and pemphigus present unique clinical as well as histological characteristics that allow for facile differentiation.

Pemphigus disorders are characterized by autoantibodies binding to desmosomes between epidermal cells, resulting in the loss of cell to cell adhesion and blister formation. In pemphigus foliaceus, autoantibodies predominantly bind to desmoglein 1, while in PV, autoantibodies bind to desmoglein 3, with some patients also forming autoantibodies to desmoglein 1 [1–4]. Antibodies targeting other keratinocyte proteins are also detected [5]. Exposure to desmoglein autoantibodies initiates cell signaling pathways resulting in keratinocytes losing their polygonal shape, detaching from neighboring cells and undergoing apoptolysis [6]. While histology shows few inflammatory cells, there is a significant amount of cell signaling activity caused by these autoantibodies, and numerous local and serum cytokine changes have been noted. When comparing desmoglein 3 reactive T-cells in human leukocyte antigen (HLA) matched family members compared to patients with pemphigus, a greater proportion of Th2 T-cells are seen, thus demonstrating the importance of differential downstream cytokine expression.

The pathogenesis of BP begins with loss of tolerance and generation of antibodies targeting BP180 and BP230, transmembrane proteins in the hemidesmosomal complexes [7]. The inception of various pro-inflammatory mediators and chemoattractants recruit immune cells

Abbreviations: AIBD, autoimmune blistering diseases; BMZ, basement membrane zone; PV, pemphigus vulgaris; PF, pemphigus foliaceus; HLA, human leukocyte antigen; SMD, standardized mean difference; CI, confidence interval; CCL, C-C chemokine ligand; CXCL, C-X-C ligand; TSLP, thymic stromal lymphopoietin; IL, interleukin; MMP, matrix metalloproteinase; DEJ, dermal-epidermal junction; CCR, C-C chemokine receptor; ECP, eosinophilic cationic protein

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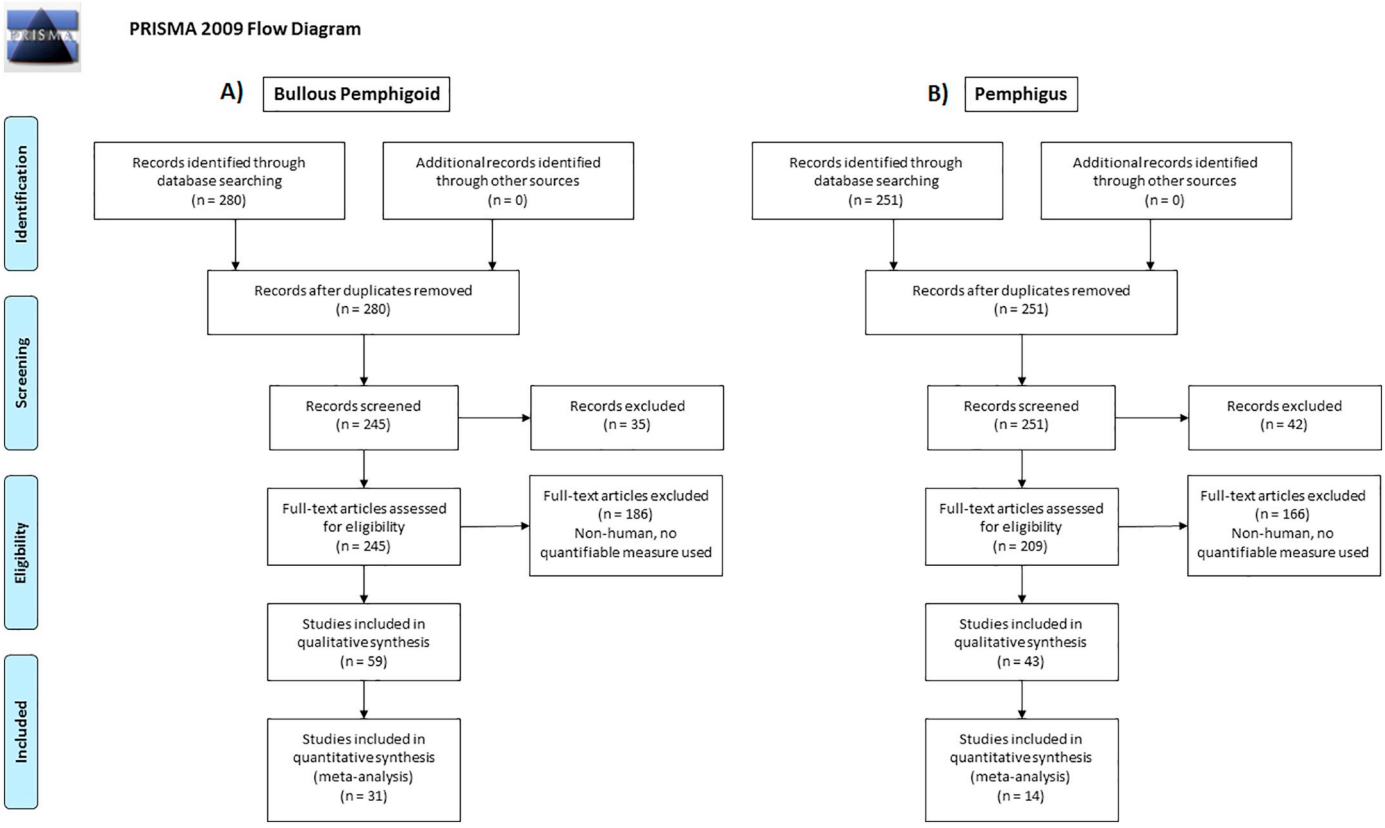

Fig. 1. PRISMA flow chart summary of literature review for (a) bullous pemphigoid and (b) pemphigus.

resulting in an inflammatory infiltrate of eosinophils, neutrophils, and lymphocytes [8]. Alterations in the BP180 protein can lead to keratinocyte thymic stromal lymphopoetin (TSLP) expression, which can result in substantial downstream signaling seen with an allergic phenotype [9].

Despite the significant increase in our knowledge of the direct mechanisms of autoantibodies with their target antigen in these diseases, the role of cytokines and chemokines remains less clear and at times inconsistent. Cytokine and chemokine abnormalities not only potentially offer a molecule for targeted treatment, but signature cytokine/chemokine changes may offer insight into causes of each disease's signature inflammatory profile. As such, we sought to comprehensively summarize the current literature regarding cytokine and chemokine levels both in serum, and locally in blister fluid in both BP and pemphigus. By performing a meta-analysis, we aimed to provide a higher level of evidence for these cytokine and chemokine discrepancies.

2. Methods

2.1. Search strategy

To characterize the cytokine and chemokine changes seen in BP and pemphigus, we performed a systematic review of the PubMed/Medline database. For search terms, we used an exhaustive list of cytokines and chemokines and pemphigus or pemphigoid. For studies on pemphigus, only PV and PF were assessed given the significant immunopathologic differences in paraneoplastic autoimmune multiorgan syndrome [10]. Due to the low number of studies measuring cytokines and chemokines in patients with pemphigus foliaceous, data is reported together for these two conditions. Inclusion criteria included studies on humans, using a quantifiable measure of serum and/or blister and chemokine levels (ELISA, densitometry, qPCR, etc.). Qualitative studies were excluded, as were animal studies. Articles were assessed by two independent reviewers, any disagreement on inclusion was resolved between the two reviewers.

2.2. Meta-analysis

To provide a higher level of evidence we performed a meta-analysis of the available studies. To be included in the meta-analysis, mean and standard deviation were requisite. In the case that median or no standard deviation were provided in the manuscript, corresponding or first authors were contacted.

Differences in mean levels of serum or blister fluid markers were used as the expected outcome. The expected outcome from each study was the difference in mean levels of serum marker between patients and control subjects. When differing control groups were used, for example, healthy controls versus other diseases, these were combined with controls unless multiple studies utilized the same control group.

Given the differences in the measurement methods and units, standardized mean difference (SMD) with 95% confidence intervals (CI) were calculated using Cohen's d in random-effects or fixed-effects models as appropriate depending on a test for heterogeneity. Significant heterogeneity of results was detected across studies as judged by a Cochrane Q statistic P value less than 0.05, I 2 statistic greater than 50%, or both. A 2-sided P value of 0.05 was taken as significant. For the calculation of SMD, cytokines levels were considered as zero when their concentration was reported to be under the detection threshold. Due to the limited number of eligible studies, subgroup analyses and meta-regression to explore potential sources of heterogeneity were not performed. Statistical analyses were conducted by using Comprehensive Meta-Analysis software (version 3.3, 2014), Englewood, NJ, USA.

2.3. Review

As a limited number of studies met criteria for inclusion in our meta-

analysis, and since only single studies existed for a majority of cytokines and chemokines, we performed a subsequent review of those studies that were not included in our meta-analysis. Likewise, we additionally evaluated studies comparing blister fluid levels to serum levels to better understand the local inflammatory network. These results are presented separately from meta-analysis results to indicate their lower level of evidence. For organizational simplicity, cytokines were divided as interleukin and non-interleukin cytokines, while chemokines were divided as C-C chemokine ligand (CCL) and C-X-C ligand (CXCL) chemokines.

3. Results

3.1. Bullous pemphigoid meta-analysis

We identified 220 eligible studies discussing BP and either cytokines or chemokines. After subsequent screening, 31 studies were included in the meta-analysis. Fig. 1a demonstrates the PRISMA flow chart for study inclusion. We identified significantly increased serum levels of Interleukin (IL)-5, IL-6, IL-8, IL-17, CCL-17, and CCL-26 in patients with BP relative to control subjects. We likewise found significantly increased blister fluids levels of IL-1α, IL-5, IL-6, IL-8, CCL11, and TNF-α. The results of the meta-analysis for BP serum and blister fluid cytokine and chemokine levels are provided in Table 1.

3.2. Pemphigus meta-analysis

We identified 251 eligible studies detailing serum and blister fluid levels of either cytokines or chemokines in pemphigus. After subsequent screening, 14 studies were included in the meta-analysis. Fig. 1b demonstrates the PRISMA flow chart for study inclusion. We identified significantly increased serum levels of IL-10, IL-17, and CCL17 in pemphigus patients relative to controls. No blister fluid studies were included in the meta-analysis. Table 2 summarizes the results of the meta-analysis in pemphigus (Table 3).

3.3. Review

Of the 73 studies detailing serum or blister fluid levels of cytokines or chemokines in BP or pemphigus, 35 did not provide mean or standard deviation. After contacting authors, we received 3 back, which were subsequently included in the meta-analysis. Thus, 32 eligible studies for the review, were not ultimately able to be included in the meta-analysis.

Several cytokines and chemokines were elevated in both serum and BP blister fluid including IL-5, IL-6, and TSLP, and CXCL8. IL-17, IL-21, IL-36, APRIL, BAFF, and TWEAK were elevated in the serum, while increased levels of IL-1α and TNF-α were increased in BP blister fluid. Blister levels of IL-2, IL-18, IL-22, IL-23, HMGB-1, IFN-γ, and CCL11 were significantly higher than BP serum levels.

Our review of the literature revealed divergent results in BP patients in regard to serum levels of IL-10, IL-23, BAFF, IFN-γ, and CXCL-9. Additionally, several cytokines and chemokines exhibited a serum to lesional gradient in BP patients. Two of these however, IL-10 and TGF-β, showed conflicting results in the literature.

In pemphigus, IL-13, IL-21, IL-27, IL-36, CCL20, CXCL 5, and VEGF were elevated in the serum. IL-6 was elevated in blister fluid of patients with pemphigus compared to patients with herpes zoster blisters. Blister levels of IL-10, IFN-γ, CXCL-8 were significantly higher compared to serum levels in patients with pemphigus.

Conflicting levels of serum cytokines were seen in pemphigus. Ten studies measured serum IFN-γ, 4 studies found reductions, 3 found elevations and 3 found no significant difference. TGF-β was elevated in 3 studies and not significantly different in 3 more. For serum IL-4, two studies found higher levels, 1 study found lower levels, while 5 studies found no significant difference. Serum IL-5 was reduced in two studies and not significantly different in another two studies. Mixed results were also seen in serum levels of IL-12, IL-15, and IL-33. Likewise, conflicting data on chemokine levels were also seen.

Serum CCL11 (Eotaxin) was reduced in three studies and not significantly altered in another study. CXCL 8 (IL-8) was elevated in pemphigus serum in 4 studies and not different in two others. Levels of CCL22, CXCL9, CXCL10 also differed between studies.

Table 1
Results of a meta-analysis performed on studies of cytokine and chemokine levels in bullous pemphigoid.

Cytokine	N of pooled studies	SMD (95% CI)	P value of SMD	I^2 statistic	P value of heterogeneity
Serum					
IL-4 vs control subjects	5	0.831 (-0.086 to 1.747)	0.076	84.72%	< 0.001
IL-5 vs control subjects	3	**2.612 (1.133 to 4.091)**	**0.001**	80.57%	0.006
IL-6 vs. control subjects	5	**2.489 (0.684 to 4.294)**	**0.007**	93.47%	< 0.001
IL-13 vs. control subjects	2	0.932 (-0.878 to 2.743)	0.313	88.12%	0.004
IL-17 vs. control subjects	3	**3.874 (2.926 to 4.823)**	**< 0.001**	56.73%	0.054
IL-31 vs. control subjects	3	1.474 (-3.733 to 6.681)	0.579	98.66%	< 0.001
IL-31 vs. dermatitis herpetiformis	2	0.339 (-2.598 to 3.275)	0.821	97.91%	< 0.001
CCL17 vs. control subjects	2	**0.864 (0.357 to 1.371)**	**0.001**	24.01%	0.251
CCL24 vs. control subjects	2	0.144 (-0.219 to 0.507)	0.437	0.00%	0.964
CCL26 vs. control subjects	2	**0.730 (0.355 to 1.105)**	**< 0.001**	0.00%	0.352
CCL11 vs. control subjects	3	2.318 (-0.220 to 4.857	0.073	91.44%	< 0.001
CCL5 vs. control subjects	2	0.809 (-0.570 to 2.189)	0.250	88.38%	0.003
TNF-α vs. control subjects	3	1.120 (-3.534 to 5.775)	0.637	97.66%	< 0.001
CXCL8 (IL-8) vs. control subjects	2	**0.986 (0.490 to 1.482)**	**< 0.001**	0.00%	0.335
CXCL10 vs. control subjects	2	8.908 (-2.546 to 20.362)	0.127	97.83%	< 0.001
CCL2 vs. control subjects	2	5.443 (-3.823 to 14.710)	0.250	98.14%	< 0.001
Blister fluid					
IL-1 alpha vs. control subjects	2	**-1.319 (-1.996 to -0.642)**	**< 0.001**	0.00%	0.560
IL-1 beta vs. control subjects	2	2.357 (-0.801 to 5.516)	0.143	92.19%	< 0.001
IL-5 vs. control subjects	2	**1.817 (0.675 to 2.959)**	**0.002**	45.49%	0.176
IL-6 vs. control subjects	4	**2.118 (2.165 to 10.468)**	**0.003**	95.38%	< 0.001
IL-10 vs. control subjects	2	3.338 (-2.422 to 9.097)	0.256	95.92%	< 0.001
CCL11 vs. control subjects	2	**1.820 (0.613 to 3.028)**	**0.003**	66.22%	0.085
CXCL8 (IL-8) vs. control subjects	2	**1.477 (0.786 to 2.168)**	**< 0.001**	0.00%	0.996
TNF-α vs. control subjects	4	**2.515 (0.523 to 4.506)**	**0.013**	89.71%	< 0.001

Those cytokines or chemokines shown in bold are significant as defined as $P < 0.05$.

Table 2
Results of a meta-analysis performed on studies of cytokine and chemokine levels in pemphigus vulgaris.

Cytokine	N of pooled studies	SMD (95% CI)	P value of SMD	I^2 statistic	P value of heterogeneity
Serum					
IL-1 alpha in PV vs control subjects	2	3.688 (-1.437 to 8.813)	0.158	97.45%	< 0.001
IL-1 beta in PV vs control subjects	2	2.097 (-2.756 to 6.949)	0.397	98.32%	< 0.001
IL-2 in PV vs. control subjects	2	-6.892 (-17.980 to 4.195)	0.223	99.06%	< 0.001
IL-6 in PV vs. control subjects	2	1.139 (-0.281 to 2.560)	0.116	89.37%	0.002
IL-10 in PV vs. control subjects	3	**1.972 (0.305 to 3.639)**	**0.020**	95.76%	< 0.001
IL-17 in PV vs. control subjects	3	**3.050 (0.128 to 5.972)**	**0.041**	97.17%	< 0.001
IL-23 in PV vs. control subjects	2	0.992 (-0.392 to 2.376)	0.160	93.13%	< 0.001
CCL-17 in PV vs. control subjects	2	**0.697 (0.153 to 1.242)**	**0.012**	0.00%	0.851
TNF-alpha in PV vs. control subjects	3	0.785 (-0.010 to 1.580)	0.053	66.22%	0.052

Those cytokines or chemokines shown in bold are significant as defined as $P < 0.05$.

4. Discussion

Our systematic review and meta-analysis demonstrate numerous inflammatory alterations in both BP and pemphigus. We will focus on those alterations demonstrated in our meta-analysis due to their higher level of evidence. We identified significantly increased serum levels of IL-5, IL-6, IL-8, IL-17, CCL-17, and CCL-26 in patients with BP, and increased blister fluids levels of IL-5, IL-6, IL-8, CCL11, and TNF-α, with a decrease in blister fluid levels of IL-1α. In pemphigus, we identified significantly increased serum levels of IL-10, IL-17, and CCL17.

4.1. Cytokines and chemokines elevated in bullous pemphigoid

Part of the IL-1 family, IL-1α is an inflammatory cytokine constitutively expressed in epithelial, endothelial and stromal cells [11–13]. It has been shown to have increased expression in response to various inflammatory stimuli and has an established role in cutaneous inflammation, specifically neutrophilic dermatoses [14,15]. IL-1α is known to induce synthesis and proteolytic activation of matrix metalloproteinase (MMP) 9, which is produced by eosinophils and neutrophils and central to blister formation in BP [11,16,17]. Interestingly, in our meta-analysis, when compared to suction blister controls, IL-1α levels were lower in BP blister fluid. This result runs contrary to the known role of the cytokine in skin inflammation. Autoantibodies targeting IL-1α have been found in several inflammatory dermatoses however, they have not been reported in BP [18]. The more likely explanation behind this result is the difference in timing of blister fluid aspiration, induction of local inflammation during suction blister production and IL-1α degradation in BP blisters [19].

IL-5 is a cytokine known to regulate various aspects of eosinophil function including differentiation, activation, survival and degranulation [20–25]. Our results indicate a significant elevation of IL-5 in the blister fluid and serum of BP patients. Eosinophils have long been known to be the predmoninant cell in the inflammatory infiltrate of BP, and are present in the earliest stages of blister development [8,26,27]. IL-5 activated eosinophils have been recently shown to induce subepidermal blistering at the dermal-epidermal junction (DEJ) [28]. Thus, the correlation between IL-5 levels and eosinophil derived granule proteins and disease severity in BP should not be surprising given its integral role in directing eosinophil function [29]. The significance of the serum to lesional IL-5 gradient in BP can likely be explained by the release of IL-5 from mast cells, and eosinophils concentrated in the lesional inflammatory milieu [29–31]. We have demonstrated that eosinophil cationic protein (ECP) can induce keratinocyte production of IL-5, leading to a positive feedback loop which may perpetuate BP [27]. Immunotherapies aimed at neutralizing IL-5 and its receptor have been developed, mepolizumab and reslizumab for IL-5, and against the IL-5Rα chain benralizumab, for hypereosinophilic conditions [32]. To date a single clinical trial investigating mepolizumab is ongoing (NCT01705795).

Further supporting the importance in the interaction of keratinocyte and eosinophils, CCL11 (eotaxin 1) and CCL26 (eotaxin 3), potent eosinophil chemoattractants are elevated in blister fluid and serum respectively [26,28,33–36]. Both eotaxins are known to mediate eosinophil transmigration and degranulation through interaction and upregulation of the C-C chemokine receptor (CCR) 3, which is universally expressed on peripheral eosinophils [34,35,37,38]. Immunohistochemical staining has identified CCL11 and CCL26 in the epidermis and dermis of BP lesional skin [33,39]. Increased expression of CCL26 and CCL11 may explain the high concentrations of eosinophils in BP lesions. Targeting eotaxin signaling should theoretically result in decreased levels of eosinophils, decrease BMZ destruction, and cause braking of this pathologic amplifying loop of BMZ destruction and granulocyte recruitment [40,41]. We have demonstrated that ECP is also capable of inducing keratinocyte eotaxin expression, further driving a positive feedback loop [27]. Bertilimumab, an anti-eotaxin 1 monoclonal antibody, is being studied in patients with BP. (NCT02226146)

IL-6 is a complex cytokine involved in numerous aspects of inflammation, antibody production, innate and adaptive immunity [42–44]. Its production by a variety of immune and non-immune cells, such as T and B cells, keratinocytes, and eosinophils highlights its multifaceted nature [43]. Elevated levels of IL-6 were found in both the serum and blister fluid of BP patients compared to controls in our analysis. Its role in BP pathogenesis likely pertains to its proinflammatory drive, effects on Th17 cell differentiation, activation and expansion as well as maturation of B cells [43–46]. Through its actions as a differentiation signal for Th17 cells, IL-6 finds itself in an inflammatory cytokine loop by promoting Th17 function resulting in further increases in IL-6 and by acting as an as an indirect initiator of MMP-9 production. Similarly to IL-5, higher concentrations were found in blister fluid suggestive of local stimulation. These lesional elevations may also enhance the survival and maintenance of antibody producing plasma cells [47–49].

IL-8, a chemokine (CXCL8), is known to recruit and activate neutrophils [50–52]. Our analysis displayed significant elevations of this cytokine in the serum and blister fluid in BP patients. Keratinocytes treated with anti-BP180 antibodies secrete IL-8, amongst other proinflammatory cytokines [53–55]. IL-8 induced chemotaxis and activation of neutrophils stimulates production of chemoattractants, such as PAF and leukotriene B4, that result in eosinophil recruitment and trans basement membrane migration [52,56,57]. As neutrophil infiltration and degranulation is a significant culprit in skin blistering, this upregulation of IL-8 is likely to be of pathologic relevance [58,59].

TNF-α is predominantly produced by macrophages and monocytes but can also be produced by other inflammatory cells including NK cells, T lymphocytes and B lymphocytes [60–63]. In our meta-analysis, TNF-α was significantly elevated in blister fluid but not in the serum of patients with BP. Several factors suggest its role in BP blister formation. TNF-α functions to regulate acute phase proteins and induces secretion of several cytokines and chemokines including IL-1, IL-6, IL-8, GM-CSF, eotaxin-1 and MMP-9 [64–72]. TNF-α stimulates T cells in a dose-

Table 3
Summary of all studies cytokine and chemokines levels in bullous pemphigoid and pemphigus serum and blister fluid. Results for blister fluid are presented as increased or decreased relative to controls (suction blister, burn blister), or blister fluid (B) levels as compared to patient serum levels (S). Highlighted boxes indicate significance demonstrated through meta-analysis [121–183].

Cytokines	Bullous pemphigoid		Pemphigus		Chemokines	Bullous pemphigoid		Pemphigus	
Interleukins	Serum	Blister	Serum	Blister	CCL chemokines	Serum	Blister	Serum	Blister
IL-1α [19,39,121-123]	U	↓, B>S	0	-	CCL1 [124]	↑	↑	-	-
IL-1β [1,19,25,121,123,125,126]	0	0, B>S	0	-	CCL2 [127-130]	0	-	0	-
IL-2 [25,48,131-135]	0	B>S	0	-	CCL3 [129]	0	-	0	-
IL-3 [136]	0	0, B=S	-	-	CCL4 [129	0	-	0	-
IL-4 [25,48,127,131-133,135-141]	0	↑, B>S	C	-	CCL5 [8,29,127-130,142]	0	U, B<S	0	-
IL-5 [22 23,25 29,48,127,128,133,135,143]	↑	↑ B>S	C	-	CCL7 [129]	-	-	0	-
IL-6 [25,39,40,48,126-128,130,131,133,136,137,144-152]	↑	↑ B>S	0	↑	CCL8 [129]	-	-	0	-
IL-7 [133,153]	0	↓, B<S	0	-	CCL11 [21,22,33,38,39, 127-129]	0	↑, B>S	C	-
IL-9 [127]	-	-	0	-	CCL17 [119,120]	↑	↑	↑	-
IL-10 [25,98,121,122,127,128,131-133,135-137,145,153-155]	C	0, C	↑	B>S	CCL18 [156]	↑	B>S	0	-
IL-11[133]	-	-	U	U	CCL 20 [157]	-	-	↑	-
IL-12 [25,127,128,131,133,135,152]	U	U	C	-	CCL 22 [119, 157]	↑	-	C	-
IL-13 [48,127,139]	0	-	↑	-	CCL 24 [33,158]	0	0, B=S	-	-
IL-15 [127,128,159]	↑	B>S	C	-	CCL 26 [33,158]	↑	↑, B>S	-	-
IL-16 [139]	↑	↑, B>S	-	-	CCL 28 [160]	↑	-	-	-
IL-17 [40,126-128,131,137,157,161-165]	↑	B>S	↑	-	CXCL chemokines	-	-	-	-
IL-18 [125]	↑	B>S	-	-	CXCL1 [129]	0	-	0	-
IL-21 [151,166]	↑	-	↑	-	CXCL5 [167]	0	-	↑	-
IL-22 [40,126-128]	0	B>S	C	-	CXCL8 [25,39,48,121, 127,128,130, 133,137,146, 152,155,168]	↑	↑, B>S	C	B>S
IL-23 [40,126,128,163,169]	C	B>S	0	-	CXCL9 [119, 129]	C	-	C	-
IL-27 [151]	-	-	↑		CXCL10 [(5, 127-130]	0	B>S	C	-
IL-31 [170-173]	0	B>S	-	-					
IL-33 [127,128,174,175]	U	U	C	-					
IL-36 [162]	↑	-	↑	-					
Non-interleukins									
APRIL [176]	↑	-	0(176)	-					
BAFF [177,178]	C	-	0	-					
GM-CSF [136]	0	0, B=S		-					
HMGB-1 [125]	0	B>S	-	-					
IFN-γ [25,127,128,131-133, 135,137,141,152,155,179]	C	↑, B>S	C	B>S					
TGF- α [180]	0	-	-	-					
TGF-β [25,40,122,132,153,154, 157,165,181,182]	C	↓, C	C	-					
TNF-α [25, 121, 122, 127, 128, 133, 137, 138, 144-147, 149, 151-153]	0	↑, B≥S	0	0					
TSLP [9]	↑	↑	-	-					
TWEAK [130]	↑	B=S	-	-					
VEGF [183]	-	-	↑	-					

↓ - decrease levels relative to control ↑increase levels relative to control, 0 – not significantly different from control, C – conflicting between studies, U – undetectable in control and BP cases, - not studied.

dependent manner and modulates differentiation of B cells [63,73]. TNF-α also promotes endothelial cells to secrete neutrophil chemotactic factors to increase neutrophil migration into tissues [74]. Likewise, TNF-α enhances IL-2 receptor function and may play a role in the Th1 response seen in BP [75]. Furthermore, Ameglio et al demonstrated that TNF-alpha blister fluid levels directly correlated with the number of BP lesions supporting its direct contribution to BP pathogenesis [25]. Therapeutically targeting TNF-α in BP remains uncertain. To date there have been 7 cases reported of BP onset following treatment with TNF-α inhibitors 1 case of worsening of BP symptoms on treatment and 2 cases describing improvement with anti-TNF therapy [76–85].

4.2. Cytokines and chemokines elevated in pemphigus

IL-10 is produced by various subsets of CD4+ T cell including Th1, Th2, Th17, in addition to B cells, eosinophils, macrophages, and keratinocytes [86–92]. IL-10 is primarily an anti-inflammatory cytokine which inhibits the production of IL-1, TNF-alpha and IL-12 from T cells and antigen presenting cells [87,88,93,94]. However, IL-10 also has inflammatory properties and promotes B cell survival, proliferation, differentiation and immunoglobulin production [95–97]. In our meta-analysis, IL-10 was elevated in the serum of patients with pemphigus. Supporting the finding that IL-10 levels are directly correlated with disease severity and the number of lesions in patients with pemphigus [98]. This may possibly due to its effect on B cell production of IgG autoantibodies. In mouse models of PV, administration of exogenous IL-10 was unable to increase production of anti-desmoglein IgG [99]. In contrast, IL-10 -/- mice have increased susceptibility to blister formation following passive transfer of PV plasma, which is inhibited with exogenous IL-10 administration [100]. Thus IL-10 likely has a concentration dependent mechanism of action in pemphigus.

4.3. Cytokines and chemokine elevated in both bullous pemphigoid and pemphigus

IL-17 was initially found to be secreted by Th17 cells, but recent studies have found that IL-17 can also be produced by mast cells, CD4+ or CD8+ T cells, and neutrophils [40,101–103]. Although many functions have been attributed to IL-17, it is most commonly associated with the development of autoimmune conditions including autoimmune encephalomyelitis, rheumatoid arthritis, multiple sclerosis, and psoriasis [101,104–107]. We found that IL-17 is elevated in the sera of patients with BP and PV compared to controls. Its role in autoimmune blistering disorders has recently become a topic of interest. IL-17 promotes the release of IL-6, IL-8, GM-CSF, TNF-alpha, MMP-9 and MMP-13 [40,101,108–110]. Additionally, IL-17 promotes neutrophil recruitment to tissues and expression of pro-inflammatory cytokines by keratinocytes [101,109,111]. BP is predominantly Th1/Th2 mediated disease with skin blistering resulting from the formation of BP180 and BP230 autoantibodies [112]. However, autoantibody formation cannot solely explain the heavy infiltration of eosinophils and neutrophils in BP [39,113]. Thus IL-17 may play a role in the production of eosinophils and neutrophils, and in promoting neutrophil migration in BP. Likewise, recent studies have suggested a role for Th1 and Th2 cells in the pathogenesis of pemphigus although infiltration of inflammatory cells is less commonly seen [114–116]. Thus, the role of IL-17 in patients with pemphigus is less clear at this time. Whether IL-17 helps to initiate BP and pemphigus disorders or is produced as a result of the local inflammatory response is still unclear.

CCL17 is a chemokine produced by keratinocytes and dendritic cells which functions to promote migration of Th1 and Th2 cells by acting as a ligand for their CCR4 and CCR8 receptors [117,118]. In our meta-analysis we found that CCL17 is elevated in the serum of patients with BP and PV. Serum levels of CCL17 were found to correlate with disease activity in BP and pemphigus, and peripheral eosinophil count in patients with BP [119,120] Thus, CCL17 may drive Th1 and Th2 cell migration into lesional tissue whereby promoting inflammation and autoantibody formation in these both diseases. In pemphigus, CCL 17 likely induces Th1/Th2 cell migration into tissues. Th2 cells then promote autoantibody production.

Some papers reported data on both bullous pemphigoid and pemphigus and are shown separately.

Search terms used:*(pemphigus or pemphigoid) AND (interleukin or chemokine or cytokine il-1 or il-2 or il-3 or il-4 or il-5 or il-6 or il-7 or il-8 or il-9 or il-10 or il-11 or il-12 or il-13 or il-14 or il-15 il-16 or il-17 or il-18 or il-19 or il-20 or il-21 or il-22 or il-23 or il-24 or il-25 or il-26 or il-27 or il-28 or il-29 or il-30 or il-31 or il-32 or il-33 or il-34 or il-35 or il-36 or CCL1 or ccl2 or ccl3 or ccl4 or ccl5 or ccl6 or ccl7 or ccl8 or ccl9 or ccl10 or ccl11 or ccl12 or ccl13 or ccl14 or cc15 or ccl16 or ccl17 or cc18 or ccl19 or ccl20 or ccl21 or ccl22 or ccl23 or ccl24 or cc25 or ccl26 or ccl27 or ccl28 or cxcl or ccl or cxcl1 or cxcl2 or cxcl3 or cxcl4 or cxcl5 or cxcl6 or cxcl7 or cxcl8 or cxcl9 or cxcl10 or cxcl11 or cxcl12 or cxcl13 or cxcl14 or cxcl15 or cxcl16 or cxcl17 or eotaxin or RANTES or thymic stromal lymphopoietin or interferon or IFN or colony stimulating factor or colony-stimulating factor or tumor necrosis factor or TNF or transforming growth factor or TGF)*

Conflict of interest

The authors report no potential conflicts of interest.

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