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There might be a role for CD200 in the pathogenesis of autoimmune and inflammatory skin disorders

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Background: Soluble CD200 (sCD200) is a novel immuno-effective molecule, which acts to regulate inflammatory and acquired immune responses. Recently, our study group showed that sCD200 was present in serum and blister fluid in a patient with bullous pemphigoid and a patient with toxic epidermal necrolysis. We therefore planned this study to evaluate the sCD200 levels of autoimmune and inflammatory skin disorder patients and to compare them with that of healthy controls.

Maleral/Methods: Our study included 30 consecutive patients with psoriasis vulgaris, 15 with pemphigus vulgaris, and 15 healthy controls. Clinical examination and laboratory tests were performed on the same day. Psoriasis patients were also assessed with the Psoriasis Area and Severity Index (PASI) and pemphigus patients were assessed using the Pemphigus Disease Area Index (PDAI). Levels of sCD200 in the serum samples were quantified using ELISA kits.

Results: The serum sCD200 level was observed to be statistically significantly higher in patients with psoriasis vulgaris (96.7±15.8) compared to patients with pemphigus vulgaris (76.2±14.6), ($p<0.001$) and healthy controls (26.8±7.0) ($p<0.001$). The serum sCD200 levels were observed to be statistically significantly higher in patients with pemphigus vulgaris compared with that in healthy controls ($p<0.001$). In addition, there was a statistically significant correlation between serum sCD200 levels and PDAI ($r=0.987$, $p=0.001$). Nevertheless, there was no statistically significant correlation between serum sCD200 levels and PASI ($r=0.154$, $p=0.407$).

Conclusions: sCD200 might play a role in immune response in the pathogenesis of autoimmune and inflammatory skin disorders. However, it remains to be fully elucidated how sCD200 can orchestrate inflammatory response in psoriasis and pemphigus.

Key words: autoimmune • inflammatory • skin • soluble CD200 (sCD200) • psoriasis • pemphigus

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Background

CD200 is a member of the immunoglobulin gene superfamily of receptors. This molecule displays a restricted tissue distribution, including activated T and B cells. CD200 is induced by inflammatory cytokines, including TNFα, and binds to CD200R [1,2]. The consequence of this interaction is to dampen the inflammatory response, with ligation of CD200R a therapeutic target in collagen-induced arthritis [3]. Chakera et al. [4] showed that circulating T(FH) cells from patients with rheumatoid arthritis show significantly increased expression of CD200, with highest levels seen in seropositive patients and patients treated with anti-TNFα agents.

In autoimmunity, the CD200-CD200R signaling pathway has been confirmed in experimental models [5]. Rosenblum et al. [6] reported that the expression of CD200 in follicular epithelium attenuates inflammatory reactions and may play a role in maintaining immune tolerance to hair follicle-associated autoantigens. Copland et al. [7] showed that monoclonal antibody-mediated CD200 receptor signaling suppresses macrophage activation and tissue damage in experimental autoimmune uveoretinitis.

Our research group recently showed the presence of soluble CD200 in serum and blister fluid in a patient with bullous pemphigoid and demonstrated the impact of anti-IgE therapy on those levels [8]. As the second findings about CD200 in immunologic response in skin, we found that soluble CD200 (sCD200) levels were higher in blister fluid than serum in patients with toxic epidermal necrolysis [9]. We therefore planned this study to evaluate the soluble serum CD200 levels in patients with autoimmune and inflammatory skin disorders and to compare it with that of healthy controls. We also analyzed the association between the serum soluble CD200 levels and the clinical severity of the disease in these patients.

Material and Methods

Patient population

Seventy individuals were included in the study. In the study population, there were 30 consecutive patients with psoriasis vulgaris, 15 with pemphigus vulgaris, and 25 healthy controls. Before the initiation of any treatment, diagnosis of pemphigus vulgaris was confirmed by histology, direct immunofluorescence, and detection of circulating anti-desmoglein 1 and anti-desmoglein 3 autoantibodies by ELISA [10]. Pemphigus patients were also assessed for clinical severity score according to the pemphigus disease area index (PDAI) [11]. Psoriasis patients were also assessed for Psoriasis Area and Severity Index (PASI). Blood samples were taken from all patients at the time of first diagnosis. Healthy volunteers had no history of allergy/atopy, family atopy, or cardiac, liver, renal, or pulmonary diseases. The study was approved by the local ethics committee, and written informed consent was obtained from all patients and healthy volunteers.

Experimental procedures

Circulating anti-desmoglein 1 and anti-desmoglein 3 autoantibody levels were measured using desmoglein 1 and desmoglein 3 microplate ELISA kits (Euroimmun, Germany). The cut-off value for the assays was 20 RU/mL. Concentrations of sCD200 in the serum samples were quantified using an ELISA kit (Sino Biological Inc., Catalog Number: SEK10886). The results were reported as means of duplicate measurements. Blood samples for sCD200 measurement were always taken in the morning between 8 and 10 am. Participants abstained from caffeinated drinks and food for 12 h before testing. Medical history was taken on the same day.

Statistical analysis

The data are presented as means ±SEM. Statistical analyses were performed using SPSS software (version 18.0; SPSS, Chicago, IL, USA). Comparison of parameters groups was performed using the t test, the chi squared test, and ANOVA. Correlations between clinical scores and CD200 were made using bivariate Person correlation. A p value of less than 0.05 was considered statistically significant.

Results

Analysis of serum soluble CD200 levels in the study population

The serum soluble CD200 level was observed to be statistically significantly higher in patients with psoriasis vulgaris (96.7±15.8) compared with that in patients with pemphigus vulgaris (76.2±14.6) ($p<0.001$) and healthy controls (26.8±7.0) ($p<0.001$). Main demographic, clinical, and diagnostic characteristics, and CD200 levels in the study population are presented in Table 1.

Analysis of serum soluble CD200 according to the clinical severity scores

There was a statistically significant correlation between serum soluble CD200 levels and clinical severity scores for pemphigus vulgaris ($r=0.987$, $p=0.001$ for PDAI). There was no statistically significant correlation between serum soluble CD200 levels and clinical severity scores for psoriasis vulgaris ($r=0.154$, $p=0.407$ for PASI).

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Table 1. Main demographic clinical and diagnostic characteristics and CD200 levels in the study population.

	Psoriasis vulgaris (n=30)	Pemphigus vulgaris (n=15)	Healthy controls (n=25)	p-value
Age (year)	41.6±14.3	51.2±13.7	45.7±15.4	0.143**
Gender				
Women, n (%)	15 (50)	6 (40)	11 (44)	0.799*
Men, n (%)	15 (50)	9 (60)	14 (56)	
PASI	4.1±3.0	–	–	–
PDAI	–	20.8±22.2	–	–
Anti-desmoglein 3 (RU/mL) Anti-desmoglein 1 (RU/mL)	–	163.1±43.1 40.4±53.4	–	–
Serum soluble CD200 (pg/mL)	96.7±15.8	76.2±14.6	26.8±7.0	<0.001**

* chi-square test; ** ANOVA; PASI – Psoriasis Area and Severity Index; PDAI – Pemphigus patients for pemphigus Disease Area Index.

Discussion

CD200 is a novel immuno-effective molecule, both cell membrane-bound and also existing in a soluble form in serum (sCD200), which acts to regulate inflammatory and acquired immune responses through interaction with cell-bound ligands, CD200R [12]. We investigated soluble CD200, which can also be linked to apoptosis and is an immuno-effective ligand [13]. In a murine model of passive cutaneous anaphylaxis, cross-linking of CD200R1 *in vivo* produced profound suppression, greater than that seen following *in vitro* CD200R1 activation, which it was felt might reflect higher constitutive expression of CD200R1 on mast cells *in vivo* compared with cells maintained in culture, and/or the existence of other cell-cell interactions *in vivo*, which could lower the threshold for CD200R1-mediated suppression. Regardless, these data were taken to imply a potential clinical utility for CD200-CD200R1 in regulation of allergic inflammatory disease [14].

Psoriasis vulgaris is one of the most prevalent chronic, inflammatory skin disorders. This skin condition is histologically characterized by abnormal proliferation of keratinocytes and infiltration of immune cells, predominantly T cells and dendritic cells in psoriatic lesions. The majority of inflammatory cells and cytokines remain in the tissue, and a relatively small proportion can be measured in the peripheral blood, including interleukins, which have shown to be elevated in patients with cardiovascular disease, metabolic syndrome, and diabetes [15,16]. Pemphigus vulgaris is widely believed to result from the deleterious action of autoantibodies directed against desmoglein 1 and desmoglein 3, resulting in loss of cell–cell adhesion within the epidermis and increased cell apoptosis [17].

The discovery of new immunological factors and a better understanding of these disorders could help to develop new biomarkers and biological drugs against specific immunological elements that cause psoriasis and pemphigus [18,19]. In our study, there was a power correlation between CD200 levels and clinical severity, suggesting that CD200 could be of potential importance as a biomarker of autoimmune and inflammatory skin disorders. Kouno et al. [20] showed that targeted therapy is feasible and may be useful for hyperproliferative and inflammatory skin diseases. They chose TRAIL as a biological model because it inhibits activated lymphocytes and causes apoptosis of hyperproliferative keratinocytes, which are features of various skin diseases. Our study showed that CD200 could play a role in maintaining pro-inflammatory reactions or immune tolerance in autoimmune and inflammatory skin disorders. Taken together, the findings of our study and previous investigations suggest the therapeutic potential of CD200 targeting agents in the treatment of skin disorders such as psoriasis, pemphigus, and bullous pemphigoid.

In our previous study, we reported the case of a man with pruritic bullous pemphigoid and very high levels of total IgE (5000 kU/L) who was refractory to the aggressive immunosuppressive regimens (systemic steroids, daily cyclophosphamide) for BP but who responded rapidly to systemic anti-IgE (omalizumab). The circulating level of sCD200 was 48.45 pg/mL in serum and 243 pg/mL in blister fluid. SCD200 levels were higher in blister fluid than in serum. During the second month of follow-up, the patient's sCD200 level decreased to 26.7 pg/mL. After the second round of omalizumab (300 mg), the frequency of exacerbations decreased [8]. Reduction in serum levels CD200 with anti-IgE treatment suggests that CD200 could be pro-inflammatory [3,4]. In the current study, we found the highest CD200 levels

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circulating in the pemphigus patients. High levels of serum soluble CD200 affect CD200R and try to protect tissue damage during autoimmune responses. In fact, the significantly higher values in psoriasis vulgaris than in pemphigus vulgaris patients and healthy controls could also support the pro-inflammatory effect.

Conclusions

In this preliminary study we showed that CD200 might play a role in immune response in the pathogenesis of psoriasis vulgaris and pemphigus vulgaris. CD200 might useful as a biomarker and therapeutic agent in inflammatory response in autoimmune and inflammatory skin disorders. The small sample size was a study limitation. In addition, the study design does not allow establishment of a causal or temporal relationship between high CD200 levels and inflammatory skin disorders. We do not know the exact mechanism of CD200 in disease initiation and/or progression.

Declaration of interest

All authors declare that they have no conflict of interest.

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