

The impact of langerin (CD207)+ dendritic cells and FOXP3+ Treg cells in the small bowel mucosa of children with celiac disease and atopic dermatitis in comparison to children with functional gastrointestinal disorders

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In the present study we aimed to evaluate the impact of langerin (CD207)+ dendritic cells (DCs) and FOXP3+ Treg cells in the intestinal mucosa of children with celiac disease (CD) and atopic dermatitis (AD) in comparison to children with functional gastrointestinal disorders (FGD). Seventy-five children (37 male, mean age 8.4 ± 4.8 years), who randomly underwent small bowel biopsy, were studied. The CD was diagnosed in 14 children, including five persons with concomitant AD (all positive for anti-tissue transglutaminase IgA antibodies and with small bowel atrophy). Normal small bowel mucosa was found in eight patients with AD and in 53 patients with FGD. The sera of all patients were tested for total and specific IgE antibodies to food allergen panels. Staining for CD11c+, langerin (CD207)+ DCs, CD4+, and FOXP3+ Treg cells was performed on paraffin-embedded sections of biopsies using immunohistochemistry. The density of CD11c+ DCs, CD4+, and FOXP3+ Treg cells was higher in the CD patients compared to the AD and FGD patients ($p = 0.02$; $p = 0.001$). In AD, significantly higher density of CD11c+ DCs was detected in patients positive for specific IgE to food allergen panels ($p = 0.02$). The FGD patients with elevated total IgE had increased density of langerin (CD207)+ DCs compared to the patients with normal total IgE levels ($p = 0.01$). The increased density of FOXP3+ Treg cells, CD4+, cells and CD11c+ DCs was associated with CD but not with AD. The elevated level of total IgE or specific IgE to food allergens was associated with more pronounced expression of DCs, indicating a possible link between the presence of these cells in small bowel mucosa with elevated level of serum IgE.

Key words: Celiac disease; atopic dermatitis; dendritic cells; immunohistochemistry; small bowel mucosa; T reg cells.

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In recent years, considerable attention has been paid to intestinal mucosa related immune mechanisms because of their significant role in immune regulation in the case of various diseases, primarily in celiac disease (CD). So far not many studies have dealt with intestinal mucosa related immune mechanisms in other immune diseases localized elsewhere, like atopic dermatitis (AD). Importantly, these two

most common childhood immune-mediated chronic diseases occur also together relatively frequently (1–4) and the incidence of these both diseases are increasing (1, 5, 6). This indicates that these two diseases might have some common immunological traits. Indeed, CD and AD have some overlapping genetic, environmental, and immunoregulatory mechanisms that play an important role in their pathogenesis (1, 7, 8). Permeability of the intestinal mucosa has been shown to increase both in CD

and AD (9). Increased intestinal permeability, which promotes antigen transfer and local inflammatory response on the gut level, might contribute to the pathogenesis of AD (10) as it is well-established for CD (11, 12).

Still, according to a recent study by Han *et al.* (13), the skin and the intestinal mucosa may have a significant interplay in development of AD. Atopic dermatitis is among the most common chronic inflammatory skin diseases characterized by disturbance of epidermal-barrier function and IgE-mediated sensitization to food and environmental allergens (14–16). The skin of AD patients contains an increased number of IgE-bearing Langerhans cells and inflammatory dendritic epidermal cells which express the high-affinity receptor for IgE (16). The dendritic cells (DCs) play a pivotal role as the key skin cells that are responsible for maintenance of immune homeostasis in the skin of patients with AD (17, 18). At the same time, DCs are involved in the aggravation of disease-specific processes leading to T-cell activation (14). Inflammatory epidermal DCs, which appear in the inflamed skin, take up and present allergens to Th1 and Th2 cells (15, 19). There is evidence of a role of CD25⁺CD4⁺ T reg cells in suppressing T-cell response to allergens through involvement in maintenance of skin homeostasis and regulation of cutaneous immune response (20). It was shown that patients with AD have significantly increased numbers of peripheral blood T reg cells with normal immunosuppressive activity and this phenomenon was associated with disease severity (21, 22). Similarly, the role of T reg cells, most frequently characterized by the expression of transcription factor FOXP3, has been reported to be important also in the pathogenesis of CD (23). In our previous studies we have shown increased FOXP3 expression in the small bowel mucosa of children with CD and type 1 diabetes (T1D) (24, 25).

Like in the skin, the DCs play a fundamental role also in gut homeostasis. Their particular role is linked to induction of tolerance to the indigenous microflora, food, and self-antigens (26). Not only the DCs, present in different lymphoid organs associated with intestine like Payers' patches, mesenteric lymph nodes and isolated lymphoid follicles, but also the DCs present in the mucosa itself and in the intestinal lamina propria, play an important role in directing immune responses to luminal antigens (27).

More recently, the expression of langerin (CD207)⁺ DCs in the intestinal mucosa has attracted considerable interest (28, 29) although langerin was originally identified as a Langerhans cell (LC)-specific C-type lectin receptor involved in

antigen capture in the skin (30). Studies of Chang *et al.* (29) suggest a possible linkage between the skin and the gut mucosa in the development of immune response to antigens at both sites through partly overlapping mechanisms. Because the langerin (CD207)⁺ DCs are significant modulators of events in the skin, study of the function of these cells in the small bowel mucosa in children with AD and CD may be of general importance.

In the present study, we aimed to evaluate the relative impact of the langerin (CD207)⁺ dendritic cells (DCs) and the FOXP3⁺ immunoregulatory T cells (Treg cells) in the intestinal mucosa in two common childhood diseases – celiac disease (CD) and atopic dermatitis (AD) – in comparison to functional gastrointestinal disorders (FGD).

MATERIALS AND METHODS

Patients

Seventy-five patients (37 male, 38 female, mean age 8.4 ± 4.8 years), who randomly underwent small bowel biopsy at Tallinn Children's Hospital in 2008–2012 were studied. Active CD was diagnosed in 14 (mean age 6.2 ± 1.0), including five persons with concomitant AD (all with positive IgA type anti-tissue transglutaminase antibodies and with small bowel atrophy). Normal small bowel mucosa was diagnosed in eight patients with AD (mean age 7.0 ± 3.4) and in 53 patients with functional gastrointestinal disorders (FGD) (mean age 9.2 ± 5.0) who formed the control group. The sera of the control group were collected at Tallinn Children's Hospital and at the Children's Clinic of Tartu University Hospital from children who had been hospitalized with various gastrointestinal, urological, and other complaints for investigations but were found to have no inflammatory or autoimmune diseases. Any acute infection in the study subjects was excluded using C-reactive protein and white blood cell count.

The diagnosis of CD was established on the basis of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria (31).

Serum samples were collected from all patients for tissue transglutaminase IgA antibody (IgA-tTG) analysis. Based on clinical suspicion and/or seropositivity for IgA-tTG, the small bowel mucosa was assessed according to the Marsh classification (32) on the basis of biopsy samples taken by gastroduodenoscopy from the distal *duodenum*.

The diagnosis of active AD was based on clinical history and objective findings in accordance with the UK Working Party's Diagnostic Criteria for Atopic Dermatitis (33). The patients with AD were underwent endoscopy based on clinical suspicion and/or seropositivity for IgA-tTG. Although skin biopsy was not performed, none of the patients had clinical signs of dermatitis herpetiformis at the time of recruitment, and hence the diagnosis of AD was confirmed. In five patients with CD and concomitant AD, dermatitis herpetiformis was excluded by determination of IgA type anti-epidermal transglutaminase

(IgA-anti-TG3) antibodies which appeared to be negative in this group of patients (34).

Ethical considerations

The study complies with the Declaration of Helsinki and has been approved by the Ethics Review Committee for Human Research of the University of Tartu. All studied children and/or their parents gave their written informed consent to participate in the study.

IgA-tTG immunoassay using the EliA™ Celikey® IgA assay

Seventy-five serum samples were tested for IgA-tTG using a fully automated EliA™ Celikey® IgA assay (Pharmacia Diagnostics, Freiburg, Germany) according to the manufacturer's instructions. Taking account of the producer's suggestions, IgA-tTG values higher than 10 EliA U/mL were considered positive.

Total IgE and specific IgE type antibodies to food allergen panels

The sera of all patients were tested for total IgE (Roche Diagnostics, Burgess Hill, England; Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA) and compared to the age-specific reference values provided by the manufacturer. The IgE type antibodies to food allergen panels fx5 (egg white, milk, fish, wheat, peanut, soybean) and fx20 (wheat, rye, barley, rice) were measured using the ImmunoCAP Specific IgE assay (Thermo Fisher Scientific, Uppsala, Sweden). According to the manufacturer's recommendations, the values of 0.35 KU/L or higher were considered positive.

General characteristics together with clinical findings (total IgE, sIgE fx5, sIgE fx20) are presented in Table 1.

Immunohistochemistry on paraffin-embedded specimens

Double staining for CD11c and langerin (CD207)

For detection of CD11c+ DCs and langerin (CD207)+ DCs in the small bowel mucosa, formalin-fixed, paraffin-embedded biopsy specimens were studied using the avidin-biotin method (Fig. 1A). Paraffin slides were deparaffinized and antigen retrieval was performed by microwave cooking in 1 mM EDTA (Scharlau Chemie S.A., Sentmenat, Spain, pH 8.0), once at 900 W for

7 min, and twice at 440 W for 5 min. Furthermore, a plastic jar was allowed to cool for 20 min at room temperature. Endogenous peroxidase activity was quenched by incubating the slides for 30 min at room temperature in 0.5% H₂O₂ methanol. Nonspecific reactions were blocked with 2.5% normal horse serum (Vectastain ABC Kit) for 10 min at room temperature. Before incubation with primary antibodies, endogenous biotin was blocked using the Biotin blocking System Kit (DAKO, Cytomation, Carpinteria, CA, USA) for 10 min at room t°. Additionally, for

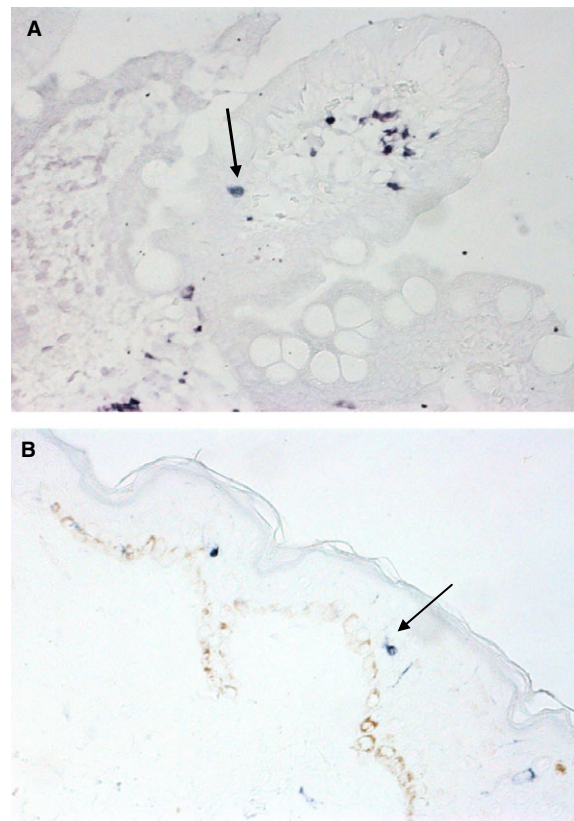


Fig. 1. (A) Double staining for CD11c (purple-red) and Langerin (CD207) (blue, arrow) on a paraffin section of the small bowel mucosa. Original magnification, 40× objective; 10× eyepiece. (B) Positive staining for Langerin (CD207)+ in the skin tissue (blue, arrow). Avidin-biotin immunoperoxidase method. Original magnification, 40× objective; 10× eyepiece.

Table 1. General and clinical characteristics of the studied patients

Study group, (n)	Mean age (years)	Elevated total IgE (>age related reference) n; (%)	sIgE fx5 ¹ positivity (>0.35 kU/L) n; (%)	sIgE fx20 ² positivity (>0.35 kU/L) n; (%)	tTGA-IgA positivity (>10 EliAU/mL) n; (%)
CD (n = 14)	6.2 ± 1.0	4 (29)	4 (29)	0	11 (79)
AD (n = 8)	7.0 ± 3.4	7 (87)	5 (63)	4 (50)	0
FGD (n = 53)	9.2 ± 5.0	20 (38)	10 (19)	6 (11)	2 (4)

¹sIgE fx5 – the IgE type antibodies to food allergen panel fx5 (egg white, milk, fish, wheat, peanut, soybean).

²sIgE fx20 – The IgE type antibodies to food allergen panel fx20 (wheat, rye, barley, rice).

blocking of the binding of antibodies to the Fc receptors, the FcR Blocking Reagent (human from Miltenyi Biotec GmbH, Germany), in dilution 1:100, for 10 min at +4 °C, was used on all studied sections.

The sections were incubated with mouse monoclonal antibodies to human CD11c (NCL-L-CD11c, clone 5D11; Leica Biosystems, Newcastle, UK) in dilution 1:80 (15 min at room temperature, then overnight at +4 °C). As the secondary antibody, biotinylated anti-mouse IgG (Vectastain ABC Kit) in dilution 1:200 was used (incubation for 30 min at room temperature). The bound antibody was detected with a commercial avidin-biotin immunoperoxidase system (Vectastain ABC Kit) according to the manufacturer's instructions, using the Vector VIP substrate kit for peroxidase as the substrate (SK-4600, Vector Laboratories, Burlingame, CA, USA) with incubation for 10 min.

The reaction was stopped by rinsing the sections in cold water, after which staining for langerin (CD207) (mouse monoclonal antibodies to human langerin (NCL-Langerin; Leica Biosystems) in dilution 1:100 in 1% horse serum (incubation for 1 h at room temperature, followed by incubation over night at 4 °C) was performed. As the secondary antibody, biotinylated anti-mouse IgG (Vectastain ABC Kit) in dilution 1:200 (incubation for 30 min at room temperature) was used. The bound antibody was detected with a commercial avidin-biotin immunoperoxidase system (Vectastain ABC Kit) according to the manufacturer's instructions, using Vector SG (Vector Laboratories) as the substrate with incubation for 10 min. Negative control was performed by omitting the primary antibody (incubation with 1% horse serum). For positive control, an adenoid tissue section for CD11c staining and skin sections for langerin (CD207) staining were used (Fig. 1B).

All sections were studied with the investigator blinded to the diagnosis data. The sections were microscopically examined using an objective of $\times 40$ and an eyepiece at $\times 10$. In each of the five different microscopic fields, cells positive for CD11c, and langerin (CD207) were counted and cell densities were expressed as the mean number of positively stained cells per field. The results of double-staining for CD11c and CD207 were analyzed in a similar manner.

Double staining for CD4 and FOXP3

For detection of CD4+ and FOXP3+ T cells in the small bowel mucosa, formalin-fixed, paraffin-embedded biopsy specimens were studied using the avidin-biotin method (Fig. 2). Paraffin slides were deparaffinized and antigen retrieval was performed by microwave cooking in 1 mM EDTA (Scharlau Chemie S.A., Sentmenat, Spain, pH 8.0), once at 900 W for 7 min, and twice at 440 W for 5 min. Furthermore, a plastic jar was allowed to cool for 20 min at room temperature. Nonspecific reactions were blocked with 2.5% normal horse serum (Vectastain ABC Kit, Vector Laboratories) for 10 min at room temperature. The sections were incubated with mouse monoclonal antibodies to human CD4 (NCL-CD4, clone 1F6; Leica Biosystems Newcastle Ltd) in dilution 1:20 in TRIS (for 1.5 h at room temperature). As the secondary antibody, biotinylated anti-mouse IgG (Vectastain ABC Kit) in dilution 1:200 (incubation for 30 min at room temperature) was used. The bound antibody was detected with a commercial

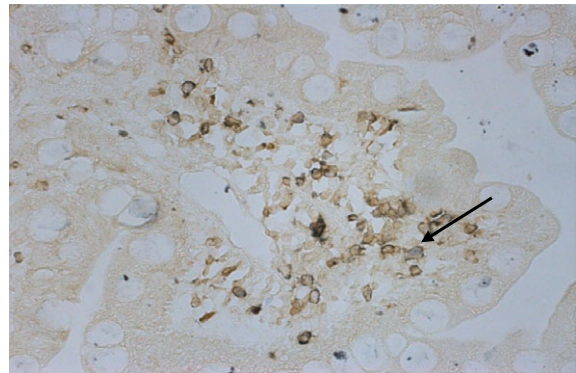


Fig. 2. Double staining for CD4 (brown) and FOXP3 (blue, arrow) on a paraffin section of the small bowel mucosa. Avidin-biotin immunoperoxidase method. Original magnification, 40 $\times$ objective; 10 $\times$ eyepiece.

avidin-biotin immunoperoxidase system (Vectastain ABC Kit) according to the manufacturer's instructions, using 3,3'-diaminobenzidine chromogen as the substrate (DAB substrate kit for peroxidase, Vector Laboratories) with incubation for 10 min.

The reaction was stopped by rinsing the sections in cold water, after which staining for FOXP3 was performed using monoclonal mouse anti-human FOXP3 antibodies (clone 236A/E7; Abcam, Cambridge, UK) in dilution 1:60 (16.6 $\mu\text{g/mL}$ in 1% normal horse serum) for 1 h at room temperature, followed by incubation overnight at +4 °C. As the secondary antibody, biotinylated anti-mouse IgG (Vectastain ABC Kit) in dilution 1:200 (incubation for 30 min at room temperature) was used. The bound antibody was detected with a commercial avidin-biotin immunoperoxidase system (Vectastain ABC Kit) according to the manufacturer's instructions, using Vector SG (Vector Laboratories) as the substrate with incubation for 10 min. The reaction was stopped by rinsing the sections in cold water, after which the sections were dehydrated and mounted in Canada balsam. Negative control was performed by omitting the primary antibody (incubation with 1% horse serum). For positive control, human tonsil sections were used.

The sections were microscopically examined using an objective of $\times 40$ and an eyepiece at $\times 10$. In each of the five different microscopic fields, T cells positive for CD4, and FOXP3 were counted and cell densities were expressed as the mean number of positively stained cells per field. The results of double-staining for CD4 and FOXP3 were analyzed in a similar manner.

Double immunohistochemical staining for CD11c and langerin (CD207) was performed in 8 AD patients, 14 CD patients, and in 38 patients with FGD.

Double immunohistochemical staining was performed for FOXP3 and CD4 in 8 AD patients, in 13 CD patients, and in 52 patients with FGD.

Statistical analysis

The results obtained for different study groups are presented as mean $\pm$ SE. Statistical calculations were carried

out with the GraphPad Prism 5.0 software using the t-test, nonparametric Mann–Whitney test, Spearman's rank correlation test and Fisher's exact test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

The general characteristics of the studied patients together with the findings of total IgE and specific IgE (sIgE fx5, sIgE fx20) are presented in Table 1.

Among the CD patients, concomitant AD was diagnosed in five children. Among the 14 CD patients, 11 children, including 4 with AD, were positive for IgA type anti-tissue transglutaminase antibodies and had partial or subtotal small bowel mucosa atrophy (Marsh grade IIIa–IIIc atrophy). Four of the 8 AD patients and 6 of the 53 FGD patients ($p = 0.006$) were sensitized to grain allergens.

Density of DCs and FOXP3+ Treg cells in the small bowel mucosa

As a new finding, we demonstrated the presence of langerin (CD207)+ DCs in the small bowel mucosa of the studied children, predominantly in those with FGD (1.19 ± 0.3 vs 0.55 ± 0.4 in CD and 0.27 ± 0.1 in AD group; $p = 0.006$) (Fig. 3A). Among the CD11c+ DCs, about 3.8% were langerin (CD207)+ as revealed by double staining. Importantly, the number of langerin (CD207)+ DCs was low in the small bowel mucosa of AD patients. Yet the number of these cells has been shown to be increased in the skin of AD patients (14). At the same time, the number of CD11c+ DCs was somewhat higher in patients with CD (23.5 ± 2.4 vs 15.9 ± 2.7 in AD and 17.1 ± 2.1 in FGD; $p = 0.02$) (Fig. 3B). The density of FOXP3+ Treg cells in the small bowel mucosa was

significantly higher in CD patients compared to AD (18.8 ± 2.9 vs 5.5 ± 2.0 ; $p = 0.001$) and FGD patients (7.0 ± 0.7 ; $p = 0.001$) (Fig. 4A). The lowest number of CD4+ cells in the small bowel mucosa was also found in patients with AD (4.5 ± 1.0 vs 13.8 ± 3.5 in CD ($p = 0.02$) and 10.9 ± 1.4 in FGD ($p = 0.0007$) (Fig. 4B).

Density of DCs and level of total and specific IgE

Notably, patients with elevated IgE levels to food antigens had differences in DCs densities in the intestinal mucosa. Thus, in the AD group, a significantly higher density of CD11c+ DCs was detected in children positive for sIgE fx5 either or for sIgE fx20 (19.9 ± 2.8 vs 9.23 ± 2.3 in sIgE neg AD; $p = 0.02$) (Fig. 5). This finding is also supported by the correlation between density of CD11c+ DCs and level of sIgE to panel fx5 in patients with AD ($r = 0.90$; $p = 0.004$).

In the FGD group, patients with elevated total IgE had a significantly higher number of langerin (CD207)+ DCs (7/12) compared to patients with normal total IgE levels (5/26) ($p = 0.01$) (Fig. 6). In the same group of patients, there was a significant correlation between level of specific IgE fx20 and density of FOXP3+ Treg cells ($r = 0.27$; $p = 0.04$), CD4+ cells ($r = 0.34$; $p = 0.01$), as well as between level of specific IgE fx5 and number of langerin (CD207)+ DCs ($r = 0.37$; $p = 0.01$).

DISCUSSION

Importantly, our study demonstrated that the increased mucosal density of FOXP3+ Treg cells, CD4+ cells, as well as CD11c+DCs was associated with CD but not with AD. However, the density of CD11c+ DCs was associated with elevated sIgE to food allergens in AD patients. Although according

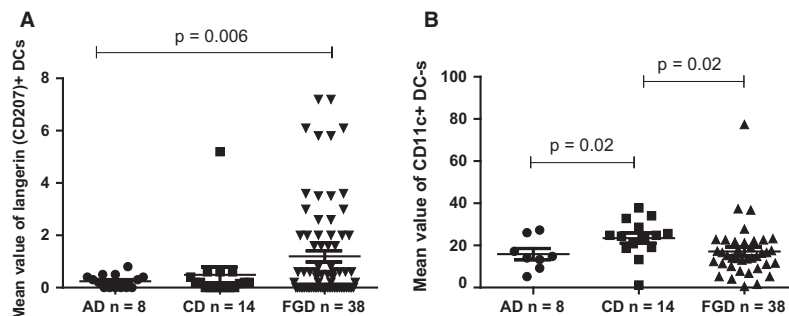


Fig. 3. (A) The density of langerin (CD207)+ DCs in paraffin sections for the different study groups. Dots represent the mean values of positively stained cells per microscopic field. Statistical analysis was carried out by using the t-test ($p = 0.006$). (B) The density of CD11c+DCs in paraffin sections for the different study groups. Dots represent the mean values of positively stained cells per microscopic field. Statistical analysis was carried out by using the t-test ($p = 0.02$).

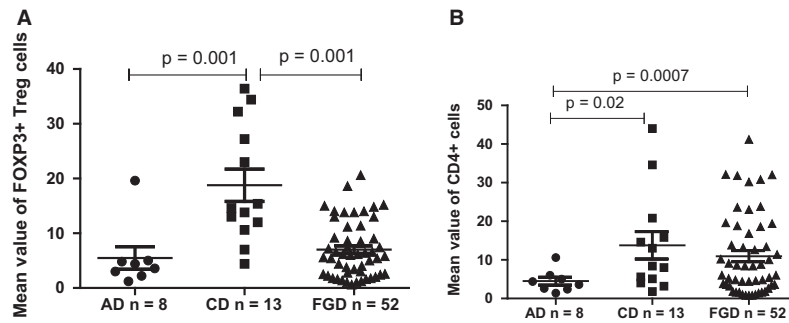


Fig. 4. (A) The density of FOXP3+ Treg cells in paraffin sections for the different study groups. Dots represent the mean values of positively stained cells per microscopic field. Statistical analysis was carried out by using the t-test ($p = 0.001$). (B) The density of CD4+ T cells in paraffin sections for the different study groups. Dots represent the mean values of positively stained cells per microscopic field. Statistical analysis was carried out by using the t-test ($p = 0.02$ and $p = 0.0007$).

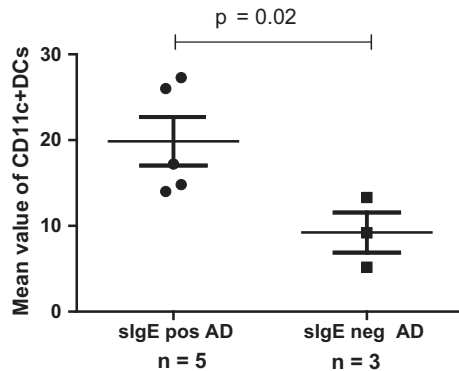


Fig. 5. The density of CD11c+ DCs in patients positive (≥ 0.35 kU/L) and negative to sIgE fx5 or fx20 in the AD group. Statistical analysis was carried out by using the t-test ($p = 0.02$).

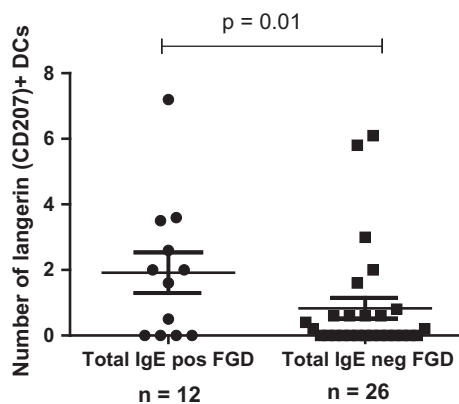


Fig. 6. The density of langerin (CD207)+ DCs in patients positive and negative for total IgE in the FGD group. Statistical analysis was carried out by using the Fisher's exact test ($p = 0.01$). The results about langerin (CD207)+ DCs ≥ 1.0 were taken into account in statistical calculations.

to our hypothesis, langerin (CD207)+ DCs could play a significant role in antigen capture in the intestinal mucosa of AD patients, we did not detect higher expression of these cells in this group of patients.

Since immunological studies of AD have so far been largely focused on the analysis of DCs and immunoregulatory mechanisms in the skin (35, 36) and peripheral blood (21, 22, 36, 37), it is difficult to draw any definitive conclusions about our findings in terms of their role in the intestinal mucosa in AD.

However, our finding about the association of density of CD11c+ DCs in the intestinal mucosa with elevated sIgE to food allergens in AD patients could indicate the possibility that not only impaired skin barrier enables allergens and microbial antigens to come into contact with DCs (14) but that also impairment of intestinal mucosal barrier and cross-linking of allergen-specific IgE molecules to intestinal DCs could play a role in the immunopathological mechanisms of AD. A study of Rentzos *et al.* (38) reported a significant increase of CD11c+ DCs and IgE-positive cells in the duodenal mucosa of birch pollen allergic patients, which is accompanied by markedly elevated IgE antibodies to pollen allergens. Moreover, according to Stary *et al.* (39) CD1a+CD11b+CD1c+ myeloid DCs in AD patients express high affinity of the IgE receptor FcER1 and cell-bound IgE on DCs obtained from both the skin and peripheral blood of AD patients.

Increased expression of FOXP3+ T reg cells in the small bowel mucosa, occurring predominantly in patients with CD, support our previous finding of the role of T reg cells in the local immune response to gluten in CD (24). However, some studies found a significant increase of circulating FOXP3+ Treg cells in patients with AD and their

correlation with serum IgE level (40). Also Roesner et al. (41) reported elevated FOXP3⁺ Treg cells expression in patients with severe AD. It should be noted that the above authors measured circulating Treg cells while in our study the density of FOXP3⁺ Treg cells was evaluated immunohistochemically.

Another important finding of our study is the ascertainment of the association of density of langerin (CD207)⁺ DCs in the small bowel mucosa with elevated levels of total IgE as well as with specific IgE to food allergens, particularly in the FGD group. A recent study of Vara et al. (42) showed that functional gastrointestinal symptoms were associated with higher total IgE level compared with that in the general population but were not associated with atopic sensitization. The authors suggested that IgE-mediated immunological mechanisms could play a role in the pathophysiology of functional gastrointestinal complaints. Presence of langerin (CD207)⁺ DCs in the small bowel mucosa could point to their role, among the other DCs, in the transportation of antigens/allergens through the epithelial layer (27). However, it is still difficult to judge from where these cells originate. Although some very recent studies show that langerin (CD207)⁺ DCs in human tissues are related to CD11c⁺ DC cells (43), this suggestion needs to be confirmed in comparison with other DCs markers. Our finding that nearly one-third of langerin (CD207)⁺ cells have also CD11c markers certainly deserves further attention as does the highest prevalence of langerin (CD207)⁺ cells in patients with FGD.

Considering that we followed strict internationally accepted diagnostic criteria in selecting AD and CD patients, excluding at the same time dermatitis herpetiformis in the studied material, we believe that our findings would still be valid for larger patient groups. Further special studies on the role of langerin (CD207)⁺ cells in the intestinal mucosa are highly awaited since langerin (CD207)⁺ DCs might play a role as significant immunomodulators in the small bowel mucosa and in the skin.

CONCLUSION

We demonstrated the absence of elevated density of intestinal mucosa FOXP3⁺ Treg cells, CD4⁺ cells, and CD11⁺ DCs in AD, unlike in CD where the numbers of these cells in the mucosa were increased. However, elevated level of total IgE or specific IgE to food allergens was associated with higher expression of CD11c⁺ and langerin (CD207)⁺ DCs in the small bowel mucosa,

indicating a possible link between the presence of these cells in the small bowel mucosa and elevated level of serum IgE.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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