

Characterization of dendritic cells from human oral mucosa: A new Langerhans' cell type with high constitutive FcεRI expression

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Background: The oral mucosa represents a unique immunologic unit with a high frequency of native allergen contact within the gastrointestinal tract in which immune tolerance is the natural outcome of allergen contact. Although Langerhans' cells (LC), known to play a crucial role in initiating allergen-dependent immune responses in the skin, have also been detected in the oral mucosa, little is known about their phenotype and exact physiologic role.

Objective: To elucidate whether LC from oral mucosa (oLC) differ from skin LC (sLC), these cells were subjected to detailed comparative analysis.

Methods: Crude epidermal and oral mucosa cell suspensions were prepared by trypsinization. oLC and sLC were compared phenotypically by flow cytometry techniques and functionally in T-cell proliferation assays.

Results: In contrast to sLC, freshly isolated oLC expressed significantly higher amounts of MHC class I and II, as well as costimulatory molecules CD40, CD80/B7.1, and CD86/B7.2. oLC displayed FcγRIII/CD16 and FcγRI/CD64. Most surprisingly, oLC constitutively expressed the high affinity receptor for IgE (FcεRI) even in nonatopic donors. FcεRI expression on oLC was further increased and correlated with the serum IgE levels in atopic individuals. oLC showed a higher allogeneic stimulatory activity than sLC, whereas the activation of autologous T cells correlated to the FcεRI expression.

Conclusion: Taken together, our results strongly indicate that oLC profoundly differ from their skin counterparts. The constitutive high expression of FcεRI on oLC could point to particular skills of these cells within the regional immune system of the oral mucosa. (*J Allergy Clin Immunol* 2003;112:141-8.)

Key words: Langerhans' cells, mucosa, high affinity receptor for IgE, Fc receptors, human

Dendritic cells (DC) form a growing complex family of bone marrow derived antigen-presenting cells. They are considered as natural adjuvants of the immune system. Typically, they reside in peripheral blood, in lymph nodes, or in peripheral tissues, mainly at interfaces between body and environment, ie, in the gut, in the airways, and in the skin in which they are known as epidermal Langerhans' cells (LC). LC play a crucial role in the afferent and the efferent limbs of the immune response and are considered as major actors involved in the initiation of primary and probably secondary immune reactions in the skin.¹

Resident human LC in normal skin contain unique cytoplasmic organelles called Birbeck granules (BG) and express a characteristic panel of surface molecules including Fc receptor for IgG (FcγRII/CD32), MHC class I and II molecules, and CD1a.¹

Little is known about the phenotype and exact physiologic role of LC found in noncornifying stratified epithelium of the oral mucosa. Because the oral cavity might be regarded as the very first compartment of the gastrointestinal tract in which immune tolerance is the natural outcome of allergen contact,² we postulated that oral mucosa LC (oLC) might differ from classic skin LC (sLC) and undertook a detailed comparative investigation of LC from skin and oral mucosa.

METHODS

Reagents

Phycoerythrin-labeled T6RD1 (IgG1; Beckman-Coulter, Krefeld, Germany) recognizes CD1a. High affinity receptor for IgE (FcεRI) was detected either by mAb 22E7 (IgG1) directed against the α-chain not interfering or mAb 15A5 (IgG1) interfering with the IgE binding site; mAb 4D8 (IgG2b) is directed against the γ-chain. These antibodies were prepared and characterized as described.^{3,4} MAbs IV.3 (IgG2b; Medarex, West Lebanon, NH) and 2E1 (IgG2a; Immunotech, Marseille, France) are directed against the low affinity IgG-receptor FcγRII/CD32. MAb 9P.25 (IgG1) reacting with the low affinity receptor for IgE FcεRII/CD23, mAb 3G8 (IgG1) against low

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Abbreviations used

7AAD: 7-Amino-actinomycin-D
 BG: Birbeck granules
 DC: Dendritic cells
 FcεRI: High affinity receptor for IgE
 oLC: Oral mucosa Langerhans' cells
 rFI: Relative fluorescence index
 rSI: Relative stimulation index
 sIgE: Serum IgE
 sLC: Skin Langerhans' cells
 surIgE: Surface bound IgE

affinity IgG-receptor FcγRIII/CD16, mAb IOT2b (IgG1) directed against HLA-DR, 67A4 (IgG1) against E-cadherin, E124.2.8 (IgG1) reacting with the Dε2 constant region of IgE, and mAb HB15a detecting CD83 (IgG2b) were from Immunotech. MAb 10.1 (IgG1) against high affinity IgG-receptor FcγRI/CD64, mAb B70/B7-2 (IgG1) directed against CD86, and mAb 5C3 (IgG1) directed against CD40 were from BD PharMingen (Hamburg, Germany). MAb W6/32 against MHC class I was provided by Dr N. Koch (Institute of Zoophysiology, University of Bonn, Germany); mAb BB-1/B7 (IgG1; Becton Dickinson, Mountain View, Calif) reacts with CD80; mAb DCGM4 (IgG1) recognizing LC-specific BG-associated lectin Langerin⁵ was provided by Dr S. Saeland (Laboratory for Immunological Research, Schering-Plough, Dardilly, France). Lag mAb (IgG1; gift of Dr Imamura, Kyoto University, Kyoto, Japan) reacts with BG-associated Lag-antigen.⁶ MAb 53103.111 is directed against chemokine-receptor-6 (CCR6) (IgG2b; R & D Systems, Minneapolis, Minn). MOPC-21 (IgG1), UPC10 (IgG2a), and MOPC-141 (IgG2b) from Sigma (Deisenhofen, Germany) and IgG1RD1 (Beckman-Coulter) were used as isotype controls. FITC-conjugated goat anti-mouse antibody was from Jackson Laboratories (West Grove, Pa). Normal mouse serum and 7-amino-actinomycin-D (7AAD) were from Sigma. Total serum IgE (sIgE) levels were determined by ELISA (Enzygnost, Marburg, Germany).

Skin and oral mucosa specimens

Human split skin (n = 51) was obtained from patients undergoing surgery at our Department of Dermatology, and specimens of oral mucosa from the vestibular region of the oral cavity (n = 73) were obtained from patients undergoing intraoral surgery at the Department of Oral and Maxillofacial Surgery. All specimens were taken from healthy sites of oral mucosa or normal skin containing no lymphoid tissue after informed consent from patients on approval of the local ethics committee. The median age of oLC donors was 34.6 ± 0.02 years and sLC donors 38.2 ± 5.05 years. Tumor patients were excluded. In some patients, 20 mL of heparinized venous blood and serum samples were drawn additionally. Atopic individuals were defined by sIgE level greater than 100 kU/L (oLC, n = 16; sLC, n = 4) with symptoms at least once a year of atopic dermatitis, allergic rhinitis, or asthma and nonatopic individuals by sIgE levels lower than 100 kU/L (oLC, n = 33; sLC, n = 10) with no symptoms of atopic diseases.

Preparation of cell suspensions

Crude epidermal cell and oral mucosa cell suspensions were prepared by trypsinization for 2 hours at 37°C as described.⁷ For short time culture 10⁶ epidermal cells or oral mucosa cells were maintained in 24-well plates (Corning, Acton, Mass) in 1 mL RPMI-1640 with Glutamax (Invitrogen, Carlsbad, Calif) supplemented with 10% heat inactivated fetal calf serum (Invitrogen), 1% antibiotics/antimycotics (Invitrogen), 5 μmol/L 2-mercaptoethanol (Sigma), and 400 U/mL GM-CSF (Novartis Pharma, Nürnberg, Germany) for 18 hours.

Immunolabeling and flow cytometric analysis of cell suspensions

An indirect triple staining for a number of 0.5 to 2 × 10⁵ unfixed viable epidermal cells or oral mucosa cells was performed as described.^{8,9} For detection of intracellular γ-chain and BG, cells were permeabilized with digitonin or saponin and analyzed by flow cytometry with FACSCalibur (Becton Dickinson) as described.¹⁰ Dead cells were excluded by 7AAD staining, and the CD1a⁺ population was gated manually. To compare the results obtained from different individuals, the relative fluorescence indexes (rFIs) of all structures were determined as follows:

$$rFI = (MFI(\text{receptor}) - MFI(\text{control})) / MFI(\text{control}),$$

where *MFI* is the mean fluorescence index.

T-cell proliferation assays

T cells were collected from patients themselves or healthy volunteers and isolated by Lymphoprep (Nyegaard, Oslo, Norway) density centrifugation as described.¹¹ As stimulator cells, triplicates of freshly isolated or cultured epidermal cells or oral mucosa cells containing 100, 500, or 1000 viable CD1a⁺ cells/well were resuspended in 100 μL RPMI-1640 and incubated with 100,000 viable allogeneic or autologous T cells in 96-well plates at 37°C. Proliferative response was measured by ³H-thymidine incorporation that was added on day 5 for 24 hours. Relative stimulation index (rSI) was calculated as follows: rSI = (cpm (mean of triplicates of coculture) – cpm (mean of triplicates of T cells)) / cpm (mean of triplicates of T cells).

Statistical analysis

Mann-Whitney *U* test and Pearson linear regression analysis were performed with the SPSS 10.0 software (SPSS, Chicago, Ill). IgE values were transformed into logarithmic files before Pearson linear regression analysis. Results are shown as arithmetic mean ± SEM. *P* values less than .05 (asterisk) or less than .01 (double asterisk) were not significant (ns).

RESULTS**oLC display typical LC features**

In a first series of experiments, freshly isolated sLC and oLC were compared by flow cytometric analysis gating cells on the basis of their CD1a expression, an antigen expressed only on LC in normal epidermis and oral mucosa.¹² The unique feature of LC, ie, the presence of BG-associated antigens Langerin and intracellular Lag, could be found in oLC but less than in sLC (Fig 1). BG in oLC was confirmed by immunoelectron microscopy (data not shown). Furthermore, both LC types expressed E-cadherin, a Ca²⁺-dependent adhesion molecule found on LC¹³ and CCR6, only expressed by immature LC and CD34⁺ precursor derived DC¹⁴ (Fig 1). Thus, oLC display typical LC features.

Fc receptor expression on LC from oral mucosa

Next we analyzed the expression of Fc receptors, characteristic for immature DC.¹ FcγRII/CD32, which has been shown to be present on sLC,^{14,15} was significantly higher expressed on oLC than sLC (Fig 2). Whereas the low affinity receptor for IgG FcγRIII/CD16 and the high affinity receptor for IgG FcγRI/CD64 were absent on sLC, both receptors were expressed on oLC. According-

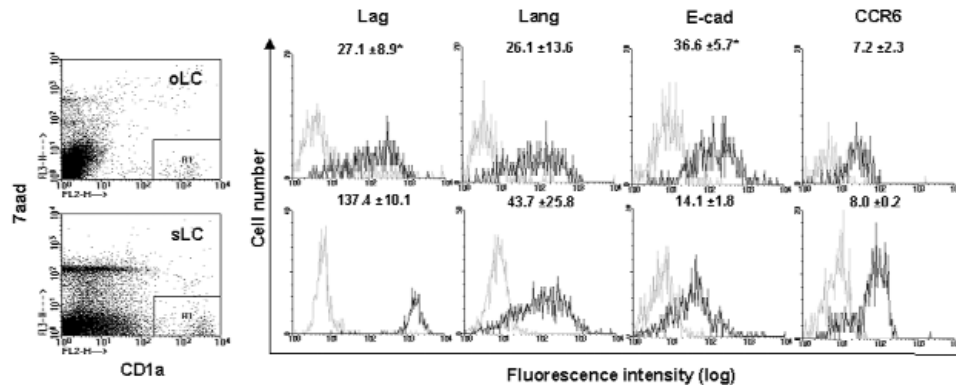


FIG 1. Analysis of typical LC markers on oLC. Dead cells were excluded by 7AAD staining, and the CD1a⁺ population was gated manually as demonstrated in 2 representative dot plots. Representative histograms of typical LC markers like Lag (*n* = 5), Langerin (*Lang*, *n* = 7), E-cadherin (*E-cad*, *n* = 5), and chemokine receptor 6 (*CCR6*, *n* = 3) on oLC (*upper panel*) and sLC (*lower panel*). RFI of all samples are placed in the upper part of each histogram (mean ± SEM).

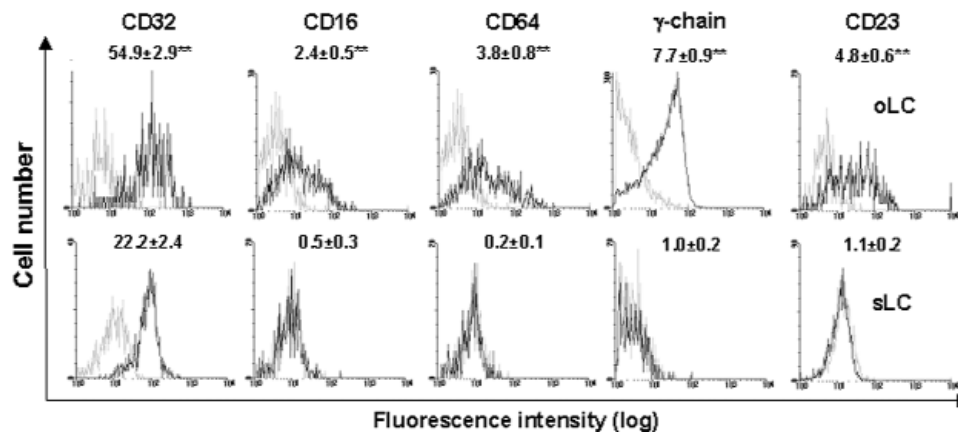


FIG 2. Expression of Fc receptors on oLC. LC were gated as demonstrated in Fig 1. Representative histograms of CD32 (oLC = 49, sLC = 14), CD16 (oLC = 11, sLC = 9), CD64 (oLC = 11, sLC = 9), γ -chain (oLC = 5, sLC = 3), and CD23 (oLC = 60, sLC = 13) of oLC (*upper panel*) and sLC (*lower panel*). RFI of all samples are placed in the upper part of each histogram (mean ± SEM).

ly, the γ -chain was detectable in oLC, its expression being mandatory for Fc γ RIII/CD16 but not reproducibly found in sLC (Fig 2). In contrast to sLC from nonatopic donors, the low affinity receptor for IgE, Fc ϵ RII/CD23, was significantly expressed on oLC (Fig 2). However, CD23 expression did not correlate with sIgE levels ($r = -0.069$, $P = .43$, $n = 37$); its expression was inconsistent because CD23 could not be detected on oLC in a substantial number of samples (20%, $n = 60$).

Constitutive expression of the high affinity receptor for IgE, Fc ϵ RI, on oLC

Besides its association with Fc γ RIII/CD16 and Fc γ RI/CD64, the γ -chain is shared with Fc ϵ RI.¹⁶ This receptor has been shown to be expressed in a trimeric form, lacking the β -chain, by antigen-presenting cells such as monocytes, LC, and other DC from atopic individuals¹⁷

but is hardly detectable on antigen-presenting cells from normal individuals. As shown in Fig 3, A, freshly isolated oLC expressed high amounts of Fc ϵ RI, corresponding with the expression of γ -chain as shown above. Most importantly, even in nonatopic donors, a remarkable expression of Fc ϵ RI was detected on oLC. This expression was even increased in oLC from atopic donors (Fig 3, A) and, as reported for sLC,⁸ Fc ϵ RI expression significantly correlated with their sIgE. In contrast, Fc ϵ RI expression on oLC from nonatopic individuals did not correlate with their sIgE (Fig 3, B). Because IgE binding to Fc ϵ RI α is one requirement for its upregulation,¹⁸ we investigated whether surface bound IgE (surIgE) is present on freshly isolated oLC. Anti-IgE staining showed variable amounts of surIgE, highest on oLC from atopic donors with high correlation between Fc ϵ RI and surIgE. On the contrary, Fc ϵ RI expression did not correlate with surIgE on oLC

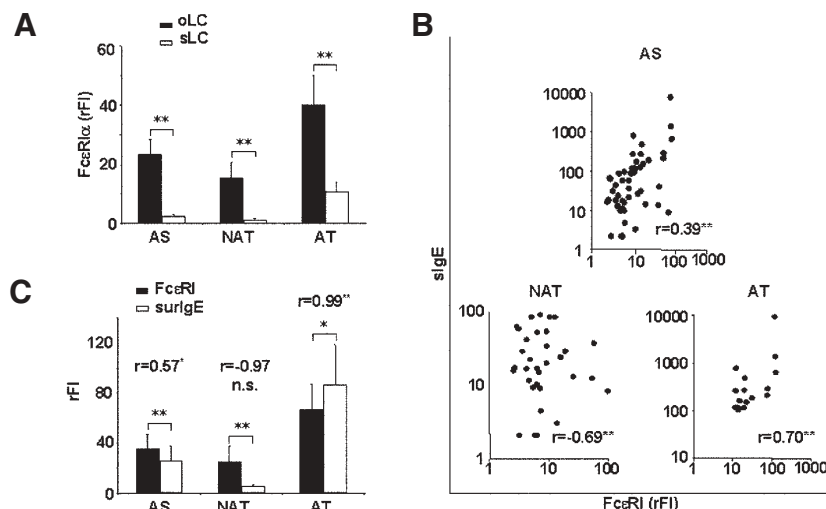


FIG 3. Investigation of FcεRI on oLC of atopic and nonatopic donors. The results are expressed as mean rFI $\pm$ SEM. **A**, Total FcεRI of all samples (AS, oLC $n = 49$, sLC $n = 40$) and FcεRI expression of samples from nonatopic (NAT, oLC $n = 33$, sLC $n = 10$) and atopic donors (AT, oLC $n = 16$, sLC $n = 4$) of oLC (closed bars) and sLC (open bars). **B**, Correlation between FcεRI expression on oLC and sIgE of all samples (AS, $n = 49$), nonatopic (NAT, $n = 33$) and atopic donors (AT, $n = 16$). **C**, SurlgE was compared to FcεRI expression on all samples of oLC (AS, $n = 16$) and in view of nonatopic status (NAT, $n = 12$) or atopic status (AT, $n = 4$). Correlation coefficient (r) of FcεRI and surlgE is placed above the bars.

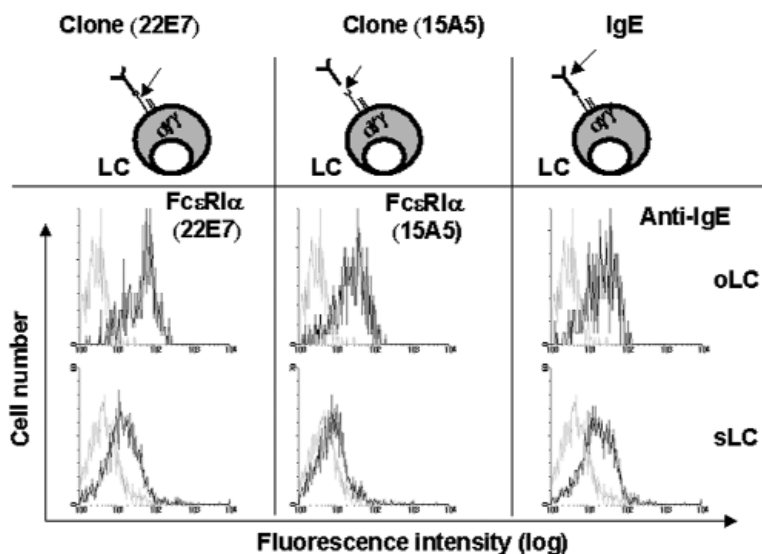


FIG 4. Detection of unoccupied FcεRI on oLC. Representative histograms of total FcεRIα expression compared to unoccupied FcεRIα expression and detection of surlgE on oLC ($n = 5$) and sLC ($n = 3$). Total FcεRIα was detected by noninhibitory mAb 22E7, unoccupied FcεRIα by inhibitory mAb 15A5, and surlgE by mAb Dε2 directed against the constant region of human IgE.

from nonatopic donors (Fig 3, C). Interestingly, in numerous samples from donors in this group surlgE was only weakly detected whereas FcεRI was strongly present, leading us to the assumption of unoccupied FcεRI. This was confirmed by using an antibody interfering with the

IgE binding site of the α -chain (15A5),³ which demonstrated high amounts of unoccupied FcεRI on oLC (Fig 4). This was in contrast to sLC in which FcεRI was not constitutively expressed. Most importantly, when FcεRI was detected on sLC from atopic individuals, unoccupied

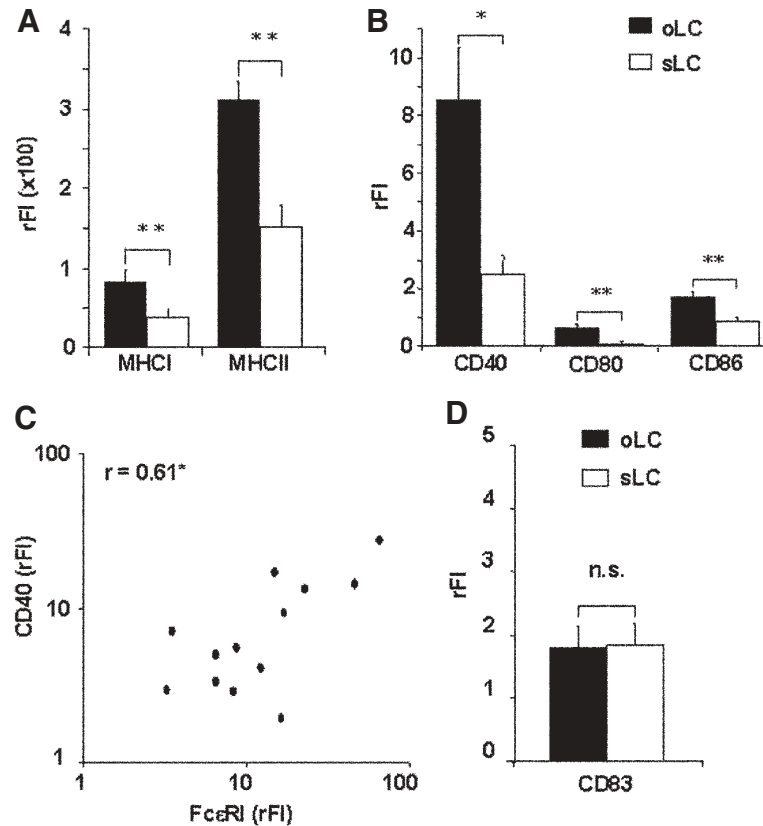


FIG 5. Comparison of MHC complexes and costimulatory molecules. oLC (closed bars) and sLC (open bars) were gated based on their CD1a expression. The results are expressed as rFI (mean ± SEM). **A**, Comparison of MHC class I (oLC n = 11, sLC n = 13) and II (oLC n = 56, sLC n = 25) complexes detected on oLC and sLC. **B**, Expression of CD40 (n = 13), CD80 (oLC n = 37, sLC n = 13), and CD86 (oLC n = 37, sLC n = 13). **C**, Correlation between CD40 and FcεRI expression on freshly isolated oLC (n = 13). **D**, CD83 (n = 8) expression of freshly isolated oLC and sLC.

receptors were hardly detectable (Fig 4). From this series of experiments we conclude that, in contrast to sLC, oLC constitutively express FcεRI.

Enhanced expression of MHC and costimulatory molecules on oLC

As members of the DC family, sLC are characterized by the expression of MHC I and II. The costimulatory molecules CD40, CD80/B7.1, and CD86/B7.2, essential for efficient T-cell priming, are weakly expressed on sLC in situ.¹⁹ Interestingly, the density of MHC I and II was significantly higher on oLC than on sLC (Fig 5, A). Moreover, CD40, CD80/B7.1, and CD86/B7.2 were expressed on both LC types but in significantly higher amounts on oLC (Fig 5, B). Interestingly, the highest CD40 expression was found on oLC from atopic donors, and its expression correlated with FcεRI expression (Fig 5, C). Conversely, CD80/B7.1 and CD86/B7.2 detected on oLC did not correlate with FcεRI expression (data not shown). CD83, a marker for mature DC,¹ was detected in

equal amounts on oLC and sLC (Fig 5, D), indicating that neither LC type is in a mature state.

Enhanced stimulatory capacity of oLC toward allogeneic but not autologous T cells in vitro

It has been shown that freshly isolated sLC are poor stimulators of allogeneic T cells but increase their stimulatory capacity after maturation during short time culture.¹ With regard to the above mentioned phenotypic differences, we explored the stimulatory activity of freshly isolated and cultured oLC and sLC. oLC were significantly more efficient in stimulating allogeneic T cells than sLC (Fig 6, A). Moreover, both LC types were less efficient in spontaneously stimulating autologous T cells (Fig 6, B). Most interestingly, freshly isolated oLC of atopic donors with high amounts of FcεRI were more potent than oLC of nonatopic donors in stimulating autologous T cells (Fig 6, C).

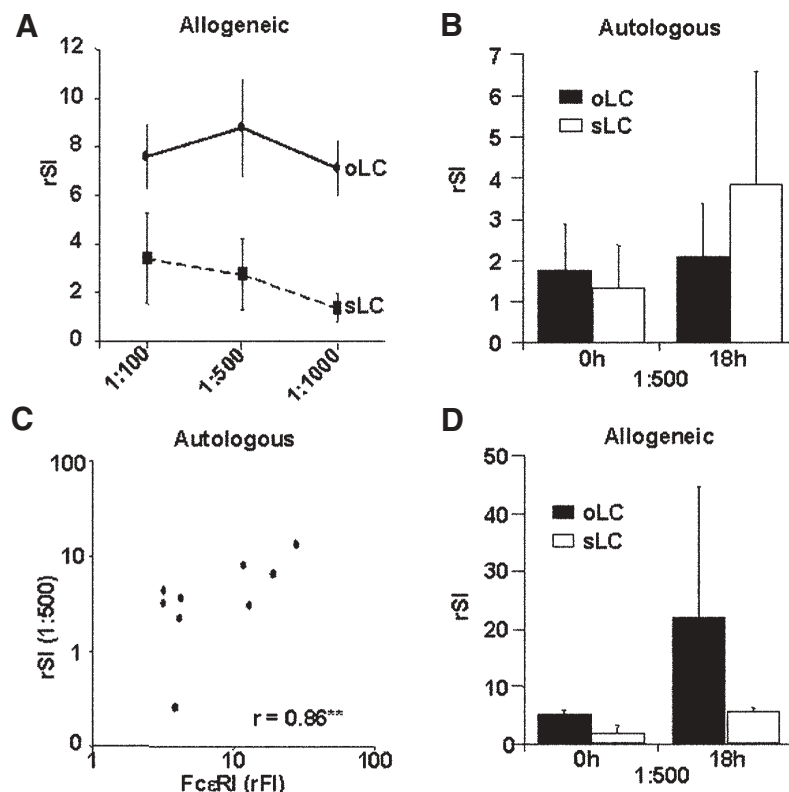


FIG 6. Investigation of allogeneic and autologous T-cell response. Results are shown as rSI. **A**, Allogeneic stimulatory capacity of freshly isolated oLC compared to sLC ($n = 5$). Mean of T-cell background proliferation (TCB), 980.2 cpm. **B**, Autologous stimulatory experiments of freshly isolated oLC and sLC and after 18 hours of culture ($n = 3$). TCB, 491 cpm. **C**, Correlation between FcεRI expression on freshly isolated oLC and autologous stimulatory capacity ($n = 9$). **D**, Allogeneic stimulatory experiments of freshly isolated oLC and sLC and after 18 hours of culture ($n = 3$). TCB, 1238.5 cpm.

After short time culture, oLC and sLC dramatically increased their stimulatory capacity toward allogeneic and autologous T cells (Fig 6, *B* and *D*) accompanied by an increase of CD83, MHC class II, and costimulatory molecules (data not shown). Thus our findings strongly indicate that, beside their phenotypical differences, oLC differ also functionally from sLC. Furthermore, oLC from atopic individuals with high amounts of FcεRI were more efficient in stimulating autologous T cells.

DISCUSSION

In this report oLC from human oral mucosa were subjected to a detailed comparative analysis with their epidermal counterparts. Although oLC display classic LC characteristics such as BG, they differ by (1) a constitutive surface FcεRI expression, (2) the presence of other Fcγ receptors, (3) an increased expression of MHC class I and II complexes and costimulatory molecules, and finally (4) by their stimulatory activity.

In the present report we demonstrated the constitutive expression of FcεRI on oLC and provided quantitative

data showing an expression level observed only on inflammatory dendritic epidermal cells from lesional skin of patients with atopic dermatitis.⁸ In contrast to sLC, a high FcεRI expression was found even on oLC of nonatopic individuals. It has been shown recently that the presence of FcεRI-bound IgE contributes to receptor upregulation through stabilizing mechanisms.¹⁸ Indeed, we detected various amounts of surIgE especially on oLC from atopic donors. It has been reported that an increased FcεRI expression on DC of the skin correlates with increased sIgE levels.⁸ This accords with the positive correlation between FcεRI expression on oLC from atopic individuals and their sIgE levels but not with our data obtained from nonatopic individuals in whom FcεRI expression did not correlate to their sIgE levels. Nevertheless, we could demonstrate a remarkable FcεRI expression on oLC of nonatopic individuals. This and the observation of unoccupied FcεRI on oLC lead us to the assumption of other receptor stabilizing mechanisms. Recently we showed that a reducing condition is a crucial factor in the regulation of FcεRI on antigen-presenting cells, resulting in an increased FcεRI surface

expression through enhanced expression of FcεRIγ chain.²⁰ Thus, we speculate that the particular microenvironment of the oral mucosa is likely to deliver the required signals for an enhanced expression of FcεRIγ chain and thereby contributes to the observed constitutive expression of FcεRI. The appearance of Fcγ receptors might also result from the enhanced γ-chain expression. Their presence further indicates the immature character of oLC. Compared to sLC from normal skin, oLC show a stronger capacity to stimulate T cells in allogeneic MLR experiments *in vitro*, which is in accordance with data obtained from oLC in the murine system.²¹ One explanation is the higher expression of costimulatory molecules and MHC I and II complexes on freshly isolated oLC reported herein, although we could only find a correlation of MHC class II and CD40 to allogeneic stimulatory capacity (data not shown). A diverse cytokine production of both LC types could also contribute to the distinct stimulatory and functional properties. A different maturation step might conduct to this phenomenon; however, CD83 expression, known to be highly upregulated on mature DC,¹ was similar on freshly isolated oLC and sLC. Consequently, both cell types most likely reside in a comparable maturation state. This is further supported by our observation that both LC types dramatically increased their CD83 and MHC expression on *in vitro* culture (data not shown). Both LC types are poor stimulators in autologous T-cell proliferation assays, although we observed a correlation between high FcεRI expression and increased autologous T-cell proliferation, indicating a strong immunologic potential of FcεRI high bearing oLC, which might result from their enhanced CD40 expression. Nevertheless, these data contrast with the *in vivo* situation, in which mucosal inflammation as a possible consequence of higher stimulatory capacity is rare. Because a high expression of FcεRI is a particular feature of oLC and this receptor leads to the secretion of IL-10 in monocytes,²² we have to consider an FcεRI-induced secretion of IL-10 by oLC. Similarly, the production of tryptophan degrading enzyme indoleamine 2,3-dioxygenase by oLC on FcεRI activation is another conceivable anti-inflammatory signal.²³ On the other hand, the unique microenvironment within the oral mucosa might also contribute to an inflammatory suppression. Regarding the concept of semimature DC recently reviewed by Lutz et al²⁴ and in contrast to the above mentioned comparable maturation state to sLC considering CD83 expression, oLC with their high expression of MHC class I and II complexes and costimulatory molecules might represent a resident subpopulation of such semimature DC that are known to induce CD4⁺ T-regulatory cells.²⁴

The paradoxical presence of Fc receptors and the high allogeneic stimulatory activity of freshly isolated oLC indicate that these cells might have a different task to fulfill in the oral epithelia. This raises the question whether oLC play a role in the induction of oral tolerance, especially because oral desensitization has been shown recently to be as effective as classic intradermal route.^{2,25}

In view of these data a picture emerges that oLC represent a subset of LC, which phenotypically and functionally differ from classic sLC. Whether oLC play a role in the induction of oral tolerance remains a matter of speculation and should be addressed in further studies.

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