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T Cell Phenotypes of the Normal Nasal Mucosa: Induction of Th2 Cytokines and CCR3 Expression by IL-4

Stephen J. Till,* Louise A. Jopling,† Petra A. Wachholz,* Rachel L. Robson,† Shixin Qin,‡ David P. Andrew,‡ Lijun Wu,‡ Joost van Neerven,§ Timothy J. Williams,† Stephen R. Durham,* and Ian Sabroe‡

Mucosal environments such as that of the nose are points of first contact between the human organism and its environment. At these sites the immune system must be regulated to differentiate between and respond appropriately to pathogens and harmless contaminants. T cell-driven immune responses broadly fall into Th1- or Th2-type phenotypes, with increasing evidence that the recruitment of these T lymphocyte subsets is mediated by selective expression of specific chemokine receptors. We have investigated the immunology of the normal nasal mucosa. We show that nasal T cell lines from normal individuals, expanded by culture in IL-2, show reduced expression of the Th2-type cytokines IL-4 and IL-5 compared with lines derived from the blood of the same subjects. These T cells also show reduced expression of the Th2-selective chemokine receptor, CCR3, but similar levels of CCR4 compared with the blood-derived lines. This apparent suppression of Th2 cytokine and CCR3 expression by nasal T cells was reversed by addition of IL-4 to the culture medium. These data are consistent with the presence of a nasal mucosal microenvironment that suppresses Th2 responses and may represent a protective measure against atopic allergic disease in humans and a favoring of Th1 responses to infectious agents. In contrast, T cell expression of CCR1 was higher in the nose than in the blood regardless of the culture medium cytokine environment in keeping with a role for this receptor in tissue homing or lymphocyte activation. The Journal of Immunology, 2001, 166: 2303–2310.

The mucosa of the respiratory tract and intestine are important points of interaction between the environment and the immune system. In most individuals immune responses provide an appropriate response to infective agents, parasites, and environmental contaminants. However, in many individuals immune responses show a different phenotype, resulting in the development of atopy and associated allergic disease. The mechanisms underlying the development of atopy are poorly understood, but may represent a failure to form the normal adult Th1-biased immune phenotype (1).

Recent data have shown that in the human genital tract, T cells express IL-2 and IFN-γ in higher levels than seen in blood (2), suggesting that a mucosal Th1 phenotype may be the norm. However, data are less clear-cut for the nose. In the mouse, freshly isolated nasal T cells show a pronounced Th2-type phenotype (3). A comparison of human gut and nasal mucosa showed a greater CD4+/CD8- ratio in the nose. Thus, freshly isolated nasal T cells show a pronounced Th2-type phenotype (3). A comparison of human gut and nasal mucosa showed a greater CD4+/CD8- ratio in the nose. However, other studies have suggested that the majority of T cells released from respiratory epithelium are held in an inactive growth phase or unresponsive state (5, 6).

Recruitment of T cells is probably regulated by chemokines. Culture of naive T cells to induce a Th1 phenotype results in expression of the chemokine receptors CCR5 and CXCR3 on the cell surface (7). In contrast, culture with IL-4 and anti-IL-12 induces a Th2 phenotype associated with CCR3, CCR4, and CCR8 expression (8–12). CCR3 binds and signals chemokines whose expression is up-regulated in asthma and allergic rhinitis, including eotaxin, monocyte chemoattractant protein-3, and monocyte chemotactic protein-4 (13–19). There is evidence in humans that lymphocytes accumulating together with eosinophils express CCR3 (20), although in other studies of intradermal allergic inflammation in response to allergen most CCR3-positive cells in the tissues were non-lymphocytes (13).

We have investigated the functional state of the normal nasal mucosal T cell population. We investigated the cytokine synthesis and chemokine receptor expression of lymphocytes cultured from the nasal mucosa of normal individuals and compared these results to lymphocytes derived from the blood of the same subjects. We show that T cells derived from the nasal mucosa exhibit reduced Th2 cytokine production and reduced CCR3 expression compared with lymphocytes cultured from the blood of the same donor. This reduced Th2 cytokine production may be overcome by the addition of exogenous IL-4, suggesting local suppression of Th2 responses.

Materials and Methods

Materials

IL-2 and IL-4 were obtained from PeproTech EC (London, U.K.). Anti-CCR1 mAb 2D4 (IgG1 isotype), anti-CXCR3 mAb 1C6 (IgG1 isotype), anti-CCR3 mAb 7B11 (IgG2a), and anti-CCR4 mAb 2B10 (IgG2a) have been previously described (7, 21–23). Goat anti-mouse F(ab′)2 Abs conjugated to FITC were obtained from Dako (Ely, U.K.). Nonbinding IgG1 (clone MOPC-21) and IgG2a (clone UCPI-10) control Abs were purchased from Sigma (Poole, U.K.). Anti-CD28 mAb was purchased from Becton

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2 Address correspondence and reprint requests to Prof. Stephen R. Durham, National Heart and Lung Institute Division, Imperial College School of Medicine, London, U.K. SW3 6LY.
Dickinson (Cowley, U.K.). Anti-CCR5-PE mAb, anti-IFN-γ-FITC mAb, and anti-IL-4-PE mAbs were purchased from Pharmingen (Cowley, U.K.). Anti-CD4 and anti-CD8 mAbs were obtained from Becton Dickinson and Dako. Cell culture, Histopaque, and general laboratory reagents were purchased from Sigma.

Subjects and nasal biopsy
The nine subjects (five men and four women) recruited for this study were required to have no current nasal symptoms and a life-long absence of any symptoms indicative of sinusitis or allergic diseases such as allergic rhinitis or asthma. All subjects had negative skin prick tests to a range of 12 common aeroallergens in the presence of negative (diluent) and positive (histamine) controls. Their ages were 21–36 years, and their serum IgE limits of assay detection were approximately 10 pg/ml.

For investigation of chemokine receptor expression on leukocytes in whole blood, subjects were recruited who had no personal history of atopy or allergic disorders. The study was performed with the approval of the local ethics committee (St. Mary’s Hospital, London, U.K.).

Culture of T cells from nasal tissue and peripheral blood
Nasal biopsies were immediately halved and placed in separate wells of a 24-well culture plate containing 2 ml of complete medium and supplemented with either 10 ng/ml IL-2 alone or 10 ng/ml IL-2 together with 20 ng/ml IL-4. Autologous PBMC were isolated from heparinized blood by centrifugation over Histopaque and resuspended at 1 × 10^7 cells/ml in RPMI 1640 supplemented with 5% human AB serum, 100 U/ml penicillin, 100 μg/ml streptomycin, and 2 mM l-glutamine, subsequently referred to as complete medium. A sample of peripheral venous blood was collected before nasal biopsy.

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Characterization of cytokine expression
T cells expanded from nasal biopsies and peripheral blood were washed extensively at 5 × 10^6 cells/ml in RPMI 1640 supplemented with 10% FCS, 100 U/ml penicillin, 100 μg/ml streptomycin, and 2 mM l-glutamine. The viability of the cells was >95% as confirmed by trypan blue exclusion. Cells were then stimulated with immobilized anti-CD3 mAb (OKT3; a gift from Dr. A. Verhoef, Imperial College, London, U.K.) and anti-CD28 mAb. In some experiments the effects of comparative CD3 mAb (OKT3; a gift from Dr. A. Verhoef, Imperial College, London, U.K.) and anti-CD28 mAb. In some experiments the effects of comparative

Cytokine assays
Concentrations of IL-5, IL-4, IL-10, and IFN-γ were measured in culture supernatants of T cells. T cell lines were expanded for an additional 7 days, with fresh complete medium and cytokine added every 2–3 days.

Statistical analysis
Groups of data were compared by Student’s t test or ANOVA with Bonferroni’s post-test as appropriate using the GraphPad Prism program.

Results
Phenotypic characterization of cell lines
T cell lines were successfully raised by the expansion from eight of nine subjects of nasal and blood-derived T cells cultured in either IL-2 alone or in IL-2 in combination with IL-4. T cell lines expanded poorly in one of the nine subjects, and one of the 32 lines generated from the other eight subjects became infected, therefore, data are presented for 31 T cell lines. The numbers of cells expanded were 0.5–2.8 × 10^7 (nasal cell lines in IL-2), 1–2.2 × 10^7 (nasal cell lines in IL-2 and IL-4), 0.6–2.5 × 10^7 (blood cell lines in IL-2), and 1.9–3.5 × 10^7 (blood cell lines in IL-2 and IL-4). The expanded cell lines from nose and blood comprised almost entirely CD3^+ cells (mean, 96.7%; range, 85.2–99.5%). The CD4 and CD8 phenotypes of CD3^+ nasal and blood T cell lines are shown in Fig. 1. The majority of the nasal T cell lines, whether expanded in IL-2 or IL-2 in combination with IL-4, were of the CD3^+CD4^+ or CD3^+CD8^+ phenotypes (mean percentage of CD3^+ cells showing

3 Abbreviation used in this paper: PI, propidium iodide.
either CD4⁺ or CD8⁺ phenotypes in nasal lines grown in IL-2, 90%; nasal lines grown in IL-2 and IL-4, 90%). However, in one of the eight subjects, culture of nasal-derived T cells in the presence of IL-2 caused the expansion of CD3⁺ cells, only 63% of which stained positively with either anti-CD4 or anti-CD8 mAbs. Also, in one other subject expansion of nasal-derived T cells in the presence of IL-2 and IL-4 resulted in a CD3⁺ population, only 47.5% of which of which stained positively with either anti-CD4 or anti-CD8 mAbs. The majority of expanded cells were positive for the αβ TCR (70–96% from nasal lines expanded in IL-2 alone; n = 4).

Cytokine expression of nasal and blood T cell lines

The patterns of cytokine generation by IL-2-expanded nasal and blood T cell lines were independent of the stimulation employed to induce T cell activation. Fig. 2 shows that in four subjects nasal and blood cell lines secreted similar amounts of IFN-γ when stimulated with anti-CD3, anti-CD3 in combination with anti-CD28, or PHA in combination with PMA. Under all these stimulation conditions, nasal T cell lines showed reduced secretion of Th2 cytokines in comparison with those lines derived from blood. CD3/CD28 costimulation was chosen as the stimulation condition for subsequent analyses because it best mimicked activation by Ag through the TCR complex, with the exception of the intracellular cytokine staining for which PMA/ionomycin stimulation was employed (see Materials and Methods).

Fig. 3 shows data from eight subjects, in whom the cell lines derived from nasal tissue and blood were stimulated with anti-CD3 and anti-CD28 and their cytokine generation measured as described. Cell lines expanded from the blood by culture in IL-2 secreted both IL-4 and IL-5, in contrast to those lines expanded from nasal tissue in which little or no IL-4 and IL-5 protein secretion was detected. However, when cultured in a combination of IL-2 and IL-4 (Fig. 3), nasal-derived T cell lines significantly up-regulated their synthesis of IL-4 and IL-5 compared with those lines grown in IL-2 alone (p = 0.004 and p = 0.0003, respectively). In these culture conditions, both nasal and blood lymphocyte lines secreted similar quantities of IL-4 and IL-5 in amounts not different from those secreted by blood cells cultured in IL-2 alone. Synthesis of IFN-γ by nasal and blood cell lines showed no difference regardless of the cytokine environment in which the cell lines were cultured. IL-10 secretion was increased in nasal T cell lines compared with blood T cell lines, and this difference was most marked in the presence of IL-2 and IL-4 in the culture medium.

To investigate in more detail the numbers and phenotype of T cells secreting cytokines of interest, we investigated intracellular cytokine production of the T cell lines by flow cytometry in four subjects (Fig. 4 and Table I). The cell lines were divided into CD4⁺ and CD4⁻ phenotypes by Ab staining. CD4⁻ cells were predominately CD8⁻ T cells as noted above (except expansion of nasal lines in IL-2 in one of these four individuals caused the expansion of CD3⁻ cells, only 63% of which stained positively with either anti-CD4 or anti-CD8 mAbs). In cell lines cultured in IL-2 only, the numbers of CD4⁺ cells that were IL-4 positive and IFN-γ negative (IL-4⁻/IFN-γ⁻) were lower in nasal than peripheral blood cultures. Conversely, the numbers of CD4⁺ T cells that were IFN-γ positive but IL-4 negative (IL-4⁺/IFN-γ⁻) were significantly higher in nasal than peripheral blood T cell lines expanded in IL-2 only. Addition of IL-4 to the nasal T cell lines caused a significant decrease in the numbers of CD4⁺ IL-4⁻/IFN-γ⁻ T cells, a nonsignificant increase in CD4⁺ IL-4⁺/IFN-γ⁻ cells (in two of four individuals), and a significant increase in...
CD4^+ IL-4^-IFN-γ^- cells (in all four donors examined). In contrast, culture in the presence of IL-4 did not significantly affect the numbers of IL-4^- and/or IFN-γ^-positive CD4^+ T cells in nasal- and peripheral blood-derived T cell lines.

Chemokine receptor expression of nasal and blood T cell lines

Expression of CCR3 has been linked with the Th2 phenotype, and therefore we examined the expression of this receptor in the nasal- and blood-derived T cell lines. CCR3 was found on a mean of 18.1% of viable cells derived from blood when grown in the presence of IL-2 alone. This level of expression was not significantly different when blood-derived lines were grown in the presence of both IL-2 and IL-4 (Fig. 5). In contrast, nasal cell line expression of CCR3 was significantly lower than that in the corresponding blood lines when cultured in IL-2. However, when cultured in the presence of both IL-2 and IL-4, the nasal-derived cell lines showed a significant enhancement of CCR3 expression (p < 0.05) to levels similar to those seen in the corresponding blood-derived lines (Fig. 5).

Regulation of the expression of CCR1 on nasal- and blood-derived T cell lines showed marked differences from that of CCR3. Whereas CCR3 was expressed on blood-derived cells cultured in the presence of IL-2 alone, CCR1 expression under these culture conditions was detected primarily on the nasal-derived cell lines (mean, 12.4% expression of CCR1 on nasal lines when grown in IL-2 compared with 5.3% expression for blood-derived lines). When cultured in IL-2 and IL-4, nasal-derived cell lines showed a nonsignificant increase in CCR1 expression, with receptor expression detected on a mean of 25.5% of viable cells. In contrast, blood-derived cell lines showed no up-regulation of CCR1 expression when grown in IL-2 and IL-4, identifying a phenotypic difference between the nasal and blood cell lines that could not be resolved by culture in these cytokines.

The expression of CCR4 on the cell lines showed a different pattern from CCR1 and CCR3 above. This receptor was equally expressed on nasal- and blood-derived T cell lines when grown in IL-2 and equally (although nonsignificantly) up-regulated on nasal and blood lines when cultured in IL-2 and IL-4.

Expression of chemokine receptors on lymphocytes in whole blood

Expansion of T cell lines from blood and nose revealed marked differences in the expression of the chemokine receptors CCR1 and CCR3. In comparison, we investigated the expression of CCR1, CCR3, CCR4, CCR5, and CXCR3 on unstimulated lymphocytes in whole blood of eight normal donors. CCR1 expression was not readily detected in cell lines expanded from whole blood (Fig. 5), and Fig. 6 shows that CCR1 expression was detected only at very low levels on CD8^+ lymphocytes in whole blood of three of eight subjects. CCR3 expression was present on 21.6% of IL-2-expanded blood T cell lines, was only detected on <1% of lymphocytes in whole blood; these were predominantly CD4^+ cells. In marked contrast, CCR4 was expressed at relatively high levels (mean, 13.8%; range, 8–21%) predominantly on CD4^+ lymphocytes and at lower levels on CD8^+ cells (mean, 3.1%; range, 1–15.6%). CCR5 expression was also detected on both CD4^+ and CD8^+ lymphocytes, but at levels lower than that of CCR4, being

![Figure 3](http://www.jimmunol.org/)

**FIGURE 3.** Cytokine generation by nasal and blood T cell lines. Polyclonal T cell lines were generated as described and stimulated with anti-CD3 and anti-CD28, and the cytokine generation was measured. Each panel shows the mean ± SEM, comparing cytokine generation of the nasal and blood lines derived from each of the eight subjects (except n = 7 for blood lines expanded in IL-2 plus IL-4). The p values are indicated on the figures and in Results.

![Figure 4](http://www.jimmunol.org/)

**FIGURE 4.** Intracellular cytokine staining determined by FACS. Nasal and blood cell lines were stimulated with PMA and ionomycin, labeled with anti-CD4 mAb, permeabilized, and stained for intracellular IFN-γ (FL1, x-axis) and IL-4 (FL-2, y-axis). The panels show typical patterns of intracellular cytokine staining from one donor, showing CD4^+ nasal vs blood T cell lines (arranged in columns), cultured in IL-2 or IL-2 plus IL-4 (arranged in rows). The mean data from four subjects are displayed in Table I.
consistent with the existence of nasal populations of Th0, Th1, and Th2 cells, with smaller numbers of Th2 cells in the nose than in the blood. Culture in the presence of IL-4 results in a redistribution of these subtypes in favor of Th0 and, to a lesser extent, Th2 cells. In two nasal T cell lines (cultured from separate donors, one in the presence of IL-2, the other in the presence of IL-2 and IL-4), CD3+ cells were expanded that stained positively with neither anti-CD4 nor anti-CD8 mAbs. The presence of CD3+ CD4+ CD8− T cells has been demonstrated previously in atopic rhinitis (33, 34), and CD4− CD8+ phenotype T cells have been identified as major producers of IL-4 (35).

Since the blood-derived cells did not require IL-4 for Th2 cytokine secretion, it is interesting to speculate that the environment of the normal nonatopic nasal mucosa actively discourages the Th2 phenotype. The environment of the nose itself may in part explain the apparent Th1 bias/reduced Th2 cytokine synthesis of the local immune system. The mucosa is constantly exposed to LPS through inhalation and local microbial growth. Such LPS exposure may induce a local Th1 environment through the up-regulation of IL-12 and IFN-γ (36). In keeping with this hypothesis, successful immunotherapy for patients with atopic disease is accompanied by a decreased skin reaction to allergen associated with an increase in cells expressing mRNA for IL-12 and IFN-γ (37) and increased expression of IFN-γ and decreased expression of IL-4 in the nose (38, 39). Similarly, in asthmatic subjects there is a relative decrease in endobronchial expression of IL-12 mRNA that is restored by treatment with steroids (40).

Interestingly, our data also revealed greater synthesis of IL-10 by nasal T cells compared with blood T cells, particularly when cultured in IL-2 and IL-4. This cytokine, which may be derived from both Th1 and Th2 cells (26) and B cells and monocytes (41) can play a significant role in Th2 responses and act as an anti-inflammatory cytokine, inhibiting mucosal allergic responses (42). This phenotypic difference between nasal and blood T cells may therefore represent a further level of suppression of potentially detrimental nasal inflammatory responses.

We have shown here that polyclonal expansion of T cells from blood by culture in IL-2 reveals a population that expresses CCR3. This large CCR3+ population was not present in whole blood stained immediately after venesecion from normal donors. In contrast, significantly fewer T cells derived from nasal mucosa expressed CCR3 when cultured in IL-2 alone, and the presence of the Th2 phenotype-inducing cytokine IL-4 up-regulated CCR3 expression to levels similar to those in peripheral blood T cells. Several studies have identified the development of a Th2-type phenotype in vitro to be associated with the expression of CCR3 (8–10, 12);
however, evidence of in vivo lymphocyte CCR3 expression is limited. In the mouse one study failed to detect evidence of CCR3 expression on Th2-type lymphocytes (43), although a recent study supports a significant role for CCR3 and CCR4 Th2-type T lymphocytes in the regulation of pulmonary allergic inflammation (44). Previous data have shown that CCR3 expression is limited to Th2-type T cells and is not apparent on Th0 cells (10). CCR3 expression was not correlated with intracellular cytokine staining in this study, and thus we do not know whether CCR3 was present on the population of T cells making both IFN-γ and IL-4 (pro- sumptive Th0 cells) or only on those cells making IL-4 alone (probably Th2-committed cells). Future studies will investigate the direct correlation of chemokine receptor expression and cytokine generation in these T cell lines.

In contrast to CCR3 expression patterns, the expression of CCR4 was not significantly different between nasal and blood T cell lines in either culture condition, although in both lines there was a nonsignificant up-regulation of CCR4 expression in the presence of IL-4. CCR4 was also expressed at much higher constitutive levels than CCR3 in circulating blood lymphocytes. CCR4 has been associated with Th2-type T cells when these have been formed under strongly polarizing conditions (10, 12), but more recent data also associate CCR4 expression with both Th1- and Th2-type T cells (23). In our study, suppression of the Th2 phenotype was not associated with decreased CCR4 expression, although its expression was inducible by IL-4. Thus, these data may favor arguments that CCR4 is not a strict marker of Th2 status.

The expression of CCR1 is a further contrast between cells isolated from blood and nasal tissue. The literature contains debate about the level of CCR1 expression on T cells derived from blood,
mostly based upon functional studies examining T cell chemokinesis to RANTES and macrophage inhibitory protein-1a (45–47). Previous studies have shown that IL-2 up-regulates CCR1 expression (45, 47); however, in our study nasal T cells grown in IL-2 showed CCR1 expression, whereas blood cells, either in whole blood or cultured in IL-2 or IL-2 plus IL-4, expressed much lower levels of this receptor. This is in some contrast to a recent study that showed that CCR1 was expressed on freshly isolated naive T cells (48). Thus, CCR1 may be important in lymphocyte homing to nasal mucosa, but may also play roles other than mediating leukocyte recruitment. Taub et al. showed that signaling via CCR1 in combination with TCR engagement could stimulate T cell proliferation and IL-2 synthesis (49). The CCR1-expressing T cells seen in the nasal-derived T cell may therefore reflect a phenotypic change in tissue vs. circulating T cells and may correspond with their ability to become activated and proliferate. Recently, a small molecule antagonist of both CCR1 and CCR3 has been described (50). Such antagonists may be useful in the amelioration of atopic disease through their direct effect on T cells, reducing Th2-type T cell trafficking to the nasal mucosa via CCR1 or CCR3 and potentially T cell activation mediated via CCR1.

Our investigation of chemokine receptor of leukocytes in whole blood also revealed significant expression levels of CXCXR3, in keeping with previous observations (7). CXCXR3 along with CCR5 is thought to be expressed on Th1-type T lymphocytes and is also expressed on naive CD4+ and CD8+ T cells (48). These data suggest that a Th1 phenotype may predominate in PBLs of normal individuals. A limitation of this study was the inability to study the T cells directly in their normal environment or without cytokine/mitogen expansion. Such work has been possible with mucosal T cells from the genital tract using surgical specimens (2); however, in our studies the small size of the biopsy made such work impossible. We attempted to minimize time in culture and rounds of stimulation required to develop sufficient cells for valid analysis by studying T cell lines rather than clones (51), which would have required more expansion steps and, therefore, significantly longer time in culture. Studying T cell lines also has an additional advantage, as the entire T cell repertoire within the starting population should be represented, in contrast to T cell clones, which probably represent only a fraction of this population. Thus, these studies have for the first time cultured T cells from the nasal mucosa of normal human subjects. We have shown that the T cell repertoire present in these cells derived from normal nasal mucosa exhibits a suppressed ability to synthesize Th2 cytokines and have altered expression of chemokine receptors that may be relevant to their recruitment or activation. Further investigation of the normal nasal immune environment is likely to lead to more insights into the mechanisms of inflammation and will serve as an interesting springboard into parallel studies investigating the changes that occur in the development of the atopic phenotype in allergic rhinitis.

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References


