The Imbalance of Lymphocyte Subsets and Cytokines: Potential Immunologic Insights Into the Pathogenesis of Chronic Dacryocystitis

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PURPOSE. To explore the quantitative distributions of different lymphocyte subsets in the lacrimal sac mucosa and identify changes of Th1- and Th2-associated cytokines in the tears of patients with chronic dacryocystitis.

METHODS. Lacrimal sac mucosal specimens from patients with chronic dacryocystitis were analyzed. Hematoxylin-eosin staining and Masson staining were performed for pathologic analysis, and immunohistochemical staining was performed for the detection of CD3+, CD4+, CD8+, CD20+, Th1, and Th2 lymphocytes. Quantitative real-time PCR was performed to analyze IFN-γ and IL-4 mRNA expression. In addition, tear samples from patients with chronic dacryocystitis and healthy volunteers were collected and analyzed with an antibody array system for Th1- and Th2-associated cytokines and chemokines.

RESULTS. Different distribution patterns of lymphocyte subsets were observed in the lacrimal sac walls. Both CD20+ B lymphocytes and CD3+ T lymphocytes accumulated in organized lymphoid follicles, and CD3+ T cells were also distributed in a diffuse manner. Among the two subsets of T cells, CD4+ T cells were more abundant than CD8+ T cells. Both the immunohistochemical staining and real-time PCR results revealed significantly higher expression levels of IFN-γ than those of IL-4. The levels of Th1- and Th2-related cytokines and chemokines measured were significantly higher in the tears of patients than in those of controls.

CONCLUSIONS. The different distribution patterns of lymphocyte subsets provide insight into a potential immunologic mechanism for dacryocystitis. The cytokines secreted by Th1 or Th2 cells may play a major role in the pathogenesis of dacryocystitis and could be explored as therapeutic targets.

Keywords: chronic dacryocystitis, lacrimal duct disease, pathogenesis
New Insights in Chronic Dacryocystitis

well as their associated cytokines exhibit cooperation and cross-regulation.15 Once the balance of this cooperation and cross-regulation is disrupted, host resistance or susceptibility to infection may be impaired. Based on the immunoregulatory effects of Th1 and Th2 cells, we proposed the hypothesis that the cytokines secreted by Th1 and Th2 cells play an important role in the pathogenesis of dacryocystitis.

In the present study, we observed the pathologic manifestations of infected lacrimal sac walls and examined different lymphocytes and their associated cytokines in the infected lacrimal sac mucosa and tears. These observations reveal a relationship between immune imbalance and chronic dacryocystitis that make a foundation for further exploration of the role of Th1- and Th2-associated cytokines in the pathogenesis of dacryocystitis.

**Materials and Methods**

**Subjects**

A total of 128 patients were included in our study. All of the patients involved were diagnosed with chronic dacryocystitis and underwent endoscopic dacryocystorhinostomy (En-DCR) from November 2016 to October 2017 at the Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China. The diagnosis of dacryocystitis was based on an assessment of the lacrimal drainage system, including inspection, palpation of the lacrimal sac, dacryocytography, axial and coronary computed tomography, and diagnostic irrigation of the lacrimal system. Symptoms of epiphora and discharge that lasted more than 6 months were considered chronic. The demographics, presenting symptoms, symptom duration, laterality, and treatment experience were recorded. None of the patients included had been treated with systemic corticosteroids or other immune-modulating drugs for at least 1 month prior to surgery. Patients with chronic dacryocystitis accompanied by glaucoma, cataracts, ocular acute inflammation, or a serious systemic disease were considered unfit to undergo En-DCR and were excluded. Patients with punctal or canalicular stenosis were also excluded. For tear protein detection, 13 patients and 15 healthy volunteers were recruited from July 2017 to October 2017, and all the healthy volunteers were confirmed as having normal lacrimal duct by lacrimal passage irrigation. None of the participants had received any eye drops prior to this study. This research adhered to the tenets of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Ninth People’s Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. Informed consent was obtained from each participant before sample collection.

**Sampling of Tissue Specimens and Histologic Procedures**

The lacrimal sac walls were harvested during En-DCR. Following removal, part of the lacrimal sac was fixed in 4% formaldehyde for 24 hours, decalcified in 20% ethylenediamine tetra acetic acid, dehydrated in graded concentrations of ethanol, and embedded in paraffin. Continuous 5-μm serial sections were used for hematoxylin-eosin (H&E), Masson, and immunohistochemical staining. The remainder of the five lacrimal sac specimens was snap-frozen in liquid nitrogen and used for RNA extraction for real-time PCR analysis. The H&E- and Masson-stained sections were examined with a light microscope (BX51; Olympus Corp., Tokyo, Japan) for histopathologic features, including morphologic changes in the epithelium, intensity of inflammatory cell infiltration, degree of fibrosis, and capillary proliferation.

**Immunohistochemical Staining**

Immunohistochemical staining of the specimens was conducted using the following method. Briefly, after being fixed, dehydrated, and embedded, the sections were immersed in 10 mM citrate buffer solution and autoclaved at 121°C for 20 minutes for antigen retrieval. After natural cooling to room temperature, the sections were treated with 10% hydrogen peroxide for 15 minutes to block endogenous peroxidase activity, followed by incubation in goat serum to reduce nonspecific antibody binding. Then, the sections were incubated with the primary antibodies overnight at 4°C to identify inflammatory cells. An anti-CD3 antibody (mouse monoclonal); an anti-CD20 antibody (mouse monoclonal); an anti-CD4 antibody (mouse monoclonal); and an anti-CD8 antibody (mouse monoclonal) were obtained from Dako (Denmark). An anti-IL-1β antibody (rabbit polyclonal, ab9657) and an anti-IL4 antibody (rabbit polyclonal, ab9622) were obtained from Abcam. After washing three times in PBS (pH 7.4), the sections were incubated with a horseradish peroxidase-conjugated secondary antibody for 30 minutes at room temperature. Diaminobenzidine was used to visualize the immunoreactivity, and distilled water was used to terminate the reaction. After a 15-minute wash with flowing water, the sections were counterstained with hematoxylin and then dehydrated, mounted, and examined by a microscope. Six light micrographs were recorded at high magnification (×400) for each experiment. Notably, serial sections were used for CD3, CD4, CD8, CD20, IFN-γ, and IL-4 staining, and the same regions of each section were selected for imaging. We used commercial software (Image-Pro Plus 6.0; Media Cybernetics, Inc., Rockville, MD, USA) for image processing. In each micrograph, the integrated optical density (IOD) values of the immunohistochemically positive cells were calculated.

**Reverse Transcription PCR and Quantitative Real-Time PCR**

Total RNA was extracted from lacrimal sac mucosal tissues using a commercial reagent (TRiZol; Life Technologies, Carlsbad, CA, USA) according to the manufacturer’s protocol. The purity and amount of each RNA sample were measured with a spectrophotometer (NanoDrop 2000C; Thermo Fisher Scientific, Waltham, MA, USA). Only RNA samples with an A260/280 ratio from 1.8 to 2.0 were used to make cDNA for reverse transcription using a commercial reagent kit (Prime-Script RT; Takara Bio, Tokyo, Japan). Quantitative real-time PCR was performed in a 10-μL reaction mixture containing 1 μL of cDNA; 1 μL of primers; 5 μL of power SYBR green PCR master mix (Applied Biosystems, Paisley, UK); and 5 μL of ddH2O on a real-time PCR system (QuantStudio 6 Flex; Applied Biosystems ). The reactions were activated at 105°C, and 40 cycles of amplification (15 seconds at 95°C and 1 minute at 60°C) were performed. Each sample was tested in triplicate. For relative quantification, data were analyzed by the ΔΔCt method and normalized to the average expression of the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase. Then, relative quantities (RQs) were calculated using the following equation: RQ = 2^-ΔΔCt.

**Tear Collection and Antibody Array System**

Tears were collected from the inner canthus or the marginal tear strip of the lower lid using disposable 20-μL microcapillaries. A total of 7 to 8 μL of tears was obtained from one
eye and stored at −80 °C until examination. For the experiment, tear samples were diluted seven times with PBS, added to the well of a glass microslide, and analyzed with an antibody array system (RayBiotech G-Series Human Th1/Th2 Array 1 Kit; RayBiotech, Norcross, GA, USA) according to the manufacturer’s instructions. The array used in our study can detect seven human Th1- and Th2-related cytokines and chemokines, namely, IFN-γ, IL-4, IL-2, IL-5, IL-8, IL-13, and TNF-α. The fluorescence signals were detected by a microarray scanner (InnolScan 300; Innopsys, Carbone, France), and the raw data were analyzed by a specific analysis tool of the analysis software used (RayBiotech) for background removing and normalization processing to obtain the cytokine and chemokine profiles in the tears.

Statistical Analysis
All statistical analyses were performed using graphing software (GraphPad Prism, GraphPad Software, Inc., La Jolla, CA, USA). Based on an analysis of the distribution of the data using the Kolmogorov-Smirnov test, the data were analyzed via t-tests for normally distributed variables or the Mann-Whitney and Kruskal-Wallis tests for non-normally distributed variables. A value of P < 0.05 was considered statistically significant.

RESULTS
Descriptive Features of the Study Groups
For the pathologic studies, 128 patients (100 females and 28 males; 3.6:1) were included (the mean age was 43.29 ± 19.12 years); 11 patients (8.59%) were bilateral cases. The duration of epiphora ranged from 6 months to 50 years with the following distribution: >10 years, 57 patients (28.91%); 5 to 10 years, 19 patients (14.84%); and <5 years, 72 patients (56.25%). A total of 92 patients (71.88%) had previously been treated with other therapies, such as probing, syringing, intubation, Nd:YAG laser surgery, and antibiotic therapy, with unsatisfactory results.

For tear protein detection, a total of 28 tear samples from 13 patients (including 12 females and 1 male, whose mean age was 48.5 ± 8.8 years ranging from 34 years to 60 years) and 15 healthy volunteers (including 13 females and 2 males, whose mean age was 42.3 ± 9.2 years ranging from 26 years to 55 years) were collected and analyzed.

Epithelial Necrosis, Inflammation, and Fibrosis Were the Most Common Pathologic Changes
We first analyzed pathologic changes in the specimens from lacrimal sacs with chronic dacryocystitis. A total of 139 (128 + 11) specimens were collected for observing histopathologic morphology. Almost all specimens displayed submucosal inflammation and fibrosis in our study. Variable degree of loss of epithelial cells, ranging from detachment to necrosis to denuded epithelium, were observed regularly, while epithelial hyperplasia with 3 to 10 layers of epithelial cells (arrows) was observed in a few lacrimal sacs. Some specimens showed loss of epithelial cells (arrows). Squamous metaplasia (arrows) was detected in four specimens of lacrimal sacs (one representative image is shown). Organized lymphoid follicles with reactive germinal center (gc) and HEV were detected; (E1) showed the general morphology of organized lymphoid follicles from the low power microscope vision. (E2) is a higher magnification of the image and showing the HEV. (F) The epithelium overlying the lymphoid follicle was infiltrated by lymphocytes, forming FAE (A–D) ×400 magnification; (E1) ×100 magnification; (E2) ×400 magnification; (F) ×200 magnification.

Figure 1. Abnormal histologic morphology of the lacrimal sac mucosa. Sections of lacrimal sacs were analyzed by H&E staining. (A) Staining of normal mucosa. (B) Epithelial hyperplasia with 3 to 5 layers of epithelial cells (arrows) was observed in a few lacrimal sacs. (C) Some specimens showed loss of epithelial cells (arrows). (D) Squamous metaplasia (arrows) was detected in four specimens of lacrimal sacs (one representative image is shown). (E) Organized lymphoid follicles with reactive germinal center (gc) and HEV were detected; (E1) showed the general morphology of organized lymphoid follicles from the low power microscope vision. (E2) is a higher magnification of the image and showing the HEV. (F) The epithelium overlying the lymphoid follicle was infiltrated by lymphocytes, forming FAE (A–D) ×400 magnification; (E1) ×100 magnification; (E2) ×400 magnification; (F) ×200 magnification.
between 3 and 9 and named severe, 3). Thus, a total score (sum) was obtained for each case ranging in inflammation (CIS < 5, 5–10, > 10). For evaluating the degree of chronic inflammation in the lacrimal sac, all these three features were scored individually according to their severity (mild, moderate, severe). Then, a total score (sum) was obtained for each case ranging between 3 and 9 and named “chronic inflammatory score.” Finally, every case was grouped according to its CIS as: mild chronic inflammation (CIS < 3); moderate chronic inflammation (3 < CIS < 6); and severe chronic inflammation (CIS > 6). We stained 35 specimens for IFN-γ and IFN-γ. The immunocytochemistry results revealed significantly stronger expression of IFN-γ than that of IL-4 (IFN-γ: median = 0.145 versus IL-4: median = 0.094, P < 0.0001; Figs. 4A1, 4B2, 4C). Some specimens were even completely negative for IL-4. The results from quantitative PCR with five samples of infected lacrimal sacs showed that the mRNA levels of IFN-γ were significantly higher than those of IL-4 (IFN-γ: 0.27949 ± 0.145 versus IL-4: 0.14498 ± 0.094, P = 0.0103; Fig. 4D). Therefore, both the protein and mRNA expression levels of IFN-γ were significantly higher in dacryocystitis cases than those of dacryocystitis.
Figure 3. Immunostaining for CD3, CD20, CD4, and CD8 in the lacrimal sac mucosa. Both B and T cells were observed in the lymphoid tissues of the lacrimal sac mucosa and were immunodetected by an anti-CD3, anti-CD20, anti-CD4, or anti-CD8 antibody (the pictures of each vertical row were stained with the same antibody as indicated), and there were more CD4⁺ T cells than CD8⁺ T cells. (A1–4) Light micrographs of the immunostaining by anti-CD3, anti-CD20, anti-CD4 or anti-CD8 antibody of nodular lymphoid tissue. (B1–4) Higher magnification images of (A1–4). (C1–4) Light micrographs of the immunostaining by anti-CD3, anti-CD20, anti-CD4, or anti-CD8 antibody of diffuse lymphoid tissues. (D1–4) Higher magnification images of (C1–4). (E) Quantitative analysis of the IOD values of CD4⁺ T cells and CD8⁺ T cells (mean with 95% CI). (A1–4, C1–4) ×100 magnification; (B1–4, D1–4) ×400 magnification.
Table 4. Relationships of the Duration of Epiphora to the IOD Values of CD4 and CD8 as Well as the CD4/CD8 Ratio (Median)

<table>
<thead>
<tr>
<th>Duration of Epiphora</th>
<th>n</th>
<th>CD4</th>
<th>CD8</th>
<th>CD4/CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5 years</td>
<td>38</td>
<td>180791.0*</td>
<td>118571.0*</td>
<td>1.63824†</td>
</tr>
<tr>
<td>&gt;5 but ≤10 years</td>
<td>14</td>
<td>209762.0*</td>
<td>138765.0*</td>
<td>1.899961</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>6</td>
<td>192964.0*</td>
<td>114917.0*</td>
<td>2.23541‡</td>
</tr>
</tbody>
</table>

Kruskal-Wallis test, \( P = 0.8616 \) \( P = 0.5654 \) \( P = 0.3029 \)

* The IOD value of CD4 or CD8 on the photograph (×400).
† The ratio between IOD value of CD4 and CD8.

higher than those of IL-4, indicating that Th1 cells play a more significant regulatory role in chronic dacryocystitis.

**Th1- and Th2-Associated Cytokines Were Expressed Differently Between the Tears of Chronic Dacryocystitis Patients and Those of Healthy Controls**

To further explore the role of Th1 and Th2 cells in chronic dacryocystitis, we extended our study to additional Th1- and Th2-related cytokines. Based on the antibody array system and optical intensity level of each spot, we measured the intensities of seven Th1- and Th2-related cytokines in the patient group and the healthy control group. Our results showed that all seven cytokines were expressed significantly more strongly in the patient group than in the control group (Table 5). To identify more differentially expressed proteins (DEPs), we defined the DEPs as those with a value of \( P < 0.05 \), a fold-change in expression greater than 1.2 or less than 0.83, and a fluorescence value greater than 150. There were 5 DEPs: IL-8, IFN-\( \gamma \), and IL-4. Our exploration of tears indicates that chronic dacryocystitis influences tears and that Th1- and Th2-associated cytokines may participate in the disease.

**DISCUSSION**

Concerning the pathogenesis of chronic dacryocystitis, previous studies have suggested that loss of functional structures, such as absence of epithelial cells, fibrosis of connective tissues of the lamina propria, and shrinkage and destruction of specialized blood vessels, may exacerbate malfunctions of the tear flow mechanism and start a vicious cycle inducing dacryocystitis.\(^6,18–21\)

According to Friedrich P. Paulsen, inflammation from the eye or nose initiates swelling of the mucous membrane, destroys the helical arrangement of connective tissue fibers and the subepithelial cavernous body with reactive hyperemia, and then induces temporary occlusion of the lacrimal passage. With repeated, isolated infections, complete fibrous closure of the lumen of the efferent tear duct ultimately occurs. Our specimens in this study showed epithelial changes, a noticeable increase in the number of inflammatory cells, and fibrosis of the lamina propria, and these findings were largely in accordance with previous evidence.

The immunohistochemical staining for lymphocytes enabled observation of the LDALT, with arrangements of lymphocytes in a diffuse or organized manner situated in and closely underneath the sac epithelium. The LDALT was believed to be formed in response to infections by microorganisms or allergic reactions and has been occasionally observed in asymptomatic dacryocystitis patients.\(^6,8,22\)

It is likely that the organized form of the lymphoid tissue represents a ganglion so allergic reactions and has been occasionally encountered in asymptomatic dacryocystitis patients.\(^6,8,22\)

**FIGURE 4.** Immunostaining for IFN-\( \gamma \) and IL-4 and mRNA expression levels of IFN-\( \gamma \) and IL-4 in the lacrimal sac mucosa. (A1-2, B1-2) Lacrimal sac mucosal tissue was stained with an anti-IFN-\( \gamma \) or anti-IL-4 antibody as indicated. (C) Quantitative analysis of the IOD values of IFN-\( \gamma \) and IL-4 cells of 35 specimens (mean with 95%CL). The number of IFN-\( \gamma \) cells was significantly greater than the number of IL-4 cells. (A1, A2, B1, B2) ×400 magnification. (D) Average IFN-\( \gamma \) and IL-4 mRNA expression levels of five patients’ lacrimal sac mucosa. The mRNA levels of IFN-\( \gamma \) were significantly higher than those of IL-4.

Table 5. Expression Profiles of 7 Th1- and Th2-Associated Proteins in the Tears of the Patient Group and the Healthy Control Group

<table>
<thead>
<tr>
<th>Protein ID</th>
<th>Patient Group</th>
<th>Control Group</th>
<th>Fold-Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>939.90</td>
<td>802.97</td>
<td>1.17</td>
<td>0.0002</td>
</tr>
<tr>
<td>IL-8</td>
<td>18702.70</td>
<td>1853.56</td>
<td>10.20</td>
<td>0.0011</td>
</tr>
<tr>
<td>IFN-( \gamma )</td>
<td>980.31</td>
<td>774.37</td>
<td>1.27</td>
<td>0.0012</td>
</tr>
<tr>
<td>TNF-( \alpha )</td>
<td>925.69</td>
<td>820.47</td>
<td>1.13</td>
<td>0.005</td>
</tr>
<tr>
<td>IL-4</td>
<td>400.74</td>
<td>317.52</td>
<td>1.26</td>
<td>0.0001</td>
</tr>
<tr>
<td>IL-5</td>
<td>891.63</td>
<td>808.11</td>
<td>1.10</td>
<td>0.0002</td>
</tr>
<tr>
<td>IL-13</td>
<td>778.70</td>
<td>697.83</td>
<td>1.12</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

The values in the table were fluorescent signal values detected by a microarray scanner (Innopsys), repressing the optical intensity level of tear proteins.
the afferent arm of mucosal immunity where antigens are taken up from the environment by the specialized FAE and presented by dendritic antigen-presenting cells (APCs), while the diffuse form of the lymphoid tissue is perceived as the efferent arm of mucosal immunity. In our study, organized lymphoid tissue was observed in a minority of the specimens, and this finding was similar with the study results from Knop et al., in which they showed the predominance of the diffuse type compared with the follicular type. This result was attributed to the old age of the tissue donors, as follicles are known to shrink with age. However, in our case, this finding may be due to delay of the condition and the relatively long duration of symptoms.

At the same time, we also observed more CD4+ T cells than CD8+ T cells based on their IOD values. The T lymphocyte subset profile, particularly the CD4/CD8 ratio, is considered as an indicator of personal immune competence to infection, and the ratio varies between sexes, age groups, and disease states. Our results indicated that the mean CD4/CD8 ratio was 1.94. Considering the pathologic states, we grouped 58 patients as mild, moderate, and severe groups based on the CIS grading system and we found that the IOD values of CD4 and CD8 of each group were significantly different, and CD4 and CD8 were expressed more abundantly as the CIS increased, while the CD4/CD8 ratio did not significantly change. All three parameters had no relationship with the symptom duration. Notably, further clinical research is needed to determine the normal reference value for the CD4/CD8 ratio.

Based on the pattern of lymphocytes and previous studies, taking into account immune factors, we postulate the following pathogenic mechanism of chronic dacryocystitis. The pathogenic microorganisms from the tears activate the lymphatic system, including humoral immunity and cellular immunity. With infiltration of inflammatory cells and hyperplasia of lymphoid tissue, constriction of the lumen of the lacrimal duct and mucosal edema occur. At this stage, the lacrimal passage shows poor irrigation, though irritation can be observed on syringing. With prolongation of the disease, adhesion of the mucosa occurs, and the lumen narrows. Then, the epithelium is lost, and fibrosis gradually leads to scarring of the lacrimal passage mucosa. Finally, complete obstruction of the lacrimal duct and chronic dacryocystitis occur. Immune factors are important in the pathogenesis of the disease and warrant further research, such as investigation of Th1/Th2 status as discussed below.

It is known that the biological roles of Th1 and Th2 cells primarily involve their secreted cytokines: IFN-γ and IL-4. Certain antigens, such as bacteria and viruses, are likely to induce a predominant lymphocyte subset and cause an imbalance of Th1/Th2 status, which is usually involved in allergic diseases and autoimmune disorders. The mucosal system, including the intestinal mucosa, gastric mucosa, and nasal mucosa, is continuously exposed to millions of antigens from the environment. For protection against potential antigens, the mucosal system possesses a unique immune system in which the balance of Th1/Th2 status plays a key role. For example, it has been assumed that Crohn disease is mainly mediated by Th1 cells, while ulcerative colitis involves Th2-type inflammation. Therefore, we investigated whether Th1 or Th2 cells were contributors to chronic dacryocystitis and examined which cell subset was dominant. Our data indicated that IFN-γ was more highly expressed than IL-4 at the mRNA and protein levels, suggesting a predominant Th1 response in chronic dacryocystitis. As the limitation of only five samples that we detected for IFN-γ and IL-4 mRNA expression levels, it needs more samples to verify the results and conduct further experiments. Furthermore, the tears from patients and healthy individuals were examined in our study, and the analyses showed that all seven Th1- and Th2-associated cytokines measured were present at significantly higher concentrations in the patient group. Based on our definition, we found three DEPs. To the best of our knowledge, this is the first study to examine Th1- and Th2-associated cytokines in chronic dacryocystitis. The results suggest that Th1- and Th2-associated cytokines may play a role in the pathogenesis of dacryocystitis, and the identified DEPs may be target proteins for further exploration.

In summary, our study revealed the presence of different types of lymphocytes and a predominant Th1 response in chronic dacryocystitis. It’s an exploration of the immune factors involved in the pathogenesis of chronic dacryocystitis, and it was suggested that an imbalance of Th1/Th2 status may play a role, providing clues for future research of the role of immune response in the pathogenesis of the disease. It was still too early to get a conclusion how inflammation was involved in progression of this disease specifically although we observed a correlation between inflammation and the disease. Further research was expected to explore. And the immunotherapy was expected to be a potential method for treating dacryocystitis.

Acknowledgments

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