Tumor Necrosis Factor-α in the Retina in Acquired Immune Deficiency Syndrome

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The presence of specific cytokines and the number and distribution of leukocytes were determined in the retinas of patients with acquired immune deficiency syndrome (AIDS). Using immunohistocytochemical techniques, three retinas from patients with AIDS had focal infiltration by T-lymphocytes and macrophages. These specimens stained positively for tumor necrosis factor-α (TNF-α) in cells identified morphologically as macrophages and glial cells and showed prominent reactive gliosis. The retinas from seven other affected patients had minimal leukocytic infiltration and no TNF-α reactivity; gliosis was present in only one. The retinas from clinically normal patients without human immunodeficiency virus (HIV) contained no TNF-α-positive cells. Using in situ hybridization for HIV, four of five patients with AIDS had rare positive cells. No interferon-γ was detected in any of the retinal tissues tested. These data suggest a role for TNF-α in the development of AIDS-related retinal disease. Invest Ophthalmol Vis Sci 33:1829–1835, 1992

Approximately 58% of patients with acquired immune deficiency syndrome (AIDS) have retinal disease. Ischemic lesions are frequent with loss of pericytes, degeneration of endothelial cells, and focal occlusion of small vessels. The substantial abnormalities of the retinal microvasculature in AIDS suggest that disease progression may involve an alteration in the blood–retina barrier, leading to leukocytic infiltration and subsequent dissemination of opportunistic pathogens such as cytomegalovirus (CMV). The mechanism of the development of this AIDS-induced retinal disease is not well understood; however, it may occur without CMV infection. In studies done on brain tissue from patients with AIDS, the cells most commonly infected with human immunodeficiency virus (HIV) are macrophages, microglial cells, multinucleated cells. Endothelial cells and glial cells are rarely infected. Although HIV usually does not infect glia, severe gliosis is often apparent, suggesting indirect pathogenetic mechanisms in the induction of central nervous system (CNS) disease. The HIV-infected macrophages appear to be the most likely vehicle for HIV infection of the brain; however, once in the brain, the mechanism of HIV dissemination and tissue degeneration is not well understood.

Tumor necrosis factor-α (TNF-α) may be critical in enhancing HIV replication and spread. This cytokine has a molecular weight of 17 kD and is produced most commonly by activated macrophages and monocytes. This mechanism of the development of this AIDS-induced retinal disease is not well understood; however, it may occur without CMV infection. In studies done on brain tissue from patients with AIDS, the cells most commonly infected with human immunodeficiency virus (HIV) are macrophages, microglial cells, multinucleated cells. Endothelial cells and glial cells are rarely infected. Although HIV usually does not infect glia, severe gliosis is often apparent, suggesting indirect pathogenetic mechanisms in the induction of central nervous system (CNS) disease. The HIV-infected macrophages appear to be the most likely vehicle for HIV infection of the brain; however, once in the brain, the mechanism of HIV dissemination and tissue degeneration is not well understood.

Tumor necrosis factor-α (TNF-α) may be critical in enhancing HIV replication and spread. This cytokine has a molecular weight of 17 kD and is produced most commonly by activated macrophages and monocytes. This activation may be induced by mitogens, antigens, or binding of HIV to the CD4 receptor of monocytes. Some affected patients show elevated TNF-α levels in their sera, which may be a reflection of the increased levels of TNF-α production by HIV-infected monocytes and macrophages. This cytokine has been shown to mediate cell proliferation, cytokine production, and cytotoxicity. In addition, TNF-α can enhance HIV production directly by inducing the synthesis of cellular factors that bind to the nuclear factor kappa binding site of the HIV long terminal repeat. In the CNS, TNF-α has been detected, and astrocytes can both produce and respond to it. Rat astrocyte cultures manufacture biologically active TNF-α and the cytokine can induce astrocytic proliferation and class II antigen expression. More significantly, TNF-α also is cytotoxic to oligodendroglial cells. These data suggest that, under specific conditions, TNF-α may be present in the CNS and that astrocytes may play a significant role in the pro-
duction of this cytokine, particularly during disease progression.

In this study, we determined (1) whether or not TNF-α was present in the retinas of patients with AIDS and (2) how the presence of this cytokine correlated with retinal disease, particularly leukocytic infiltration. To accomplish this, we examined retinas from ten HIV-seropositive patients with AIDS and five HIV-negative neurologically normal control subjects to detect the presence and distribution of leukocyte subpopulations and the cytokines TNF-α and interferon-γ (IFN-γ). In three affected patients, intense TNF-α staining was found in association with macrophages and glial cells in the nerve fiber and ganglion cell layers; these three had retinal infiltration by T-lymphocytes and macrophages. In the remaining seven patients and five normal control subjects, the absence of T-cells and relatively low numbers of macrophages correlated with little or no TNF-α positivity. These data suggest a role for TNF-α in the development of AIDS-induced retinal disease.

**Materials and Methods**

**Tissue**

Fresh retinas from patients with AIDS and neurologically normal control subjects were obtained at autopsy within 24 hours postmortem. The globes were bisected horizontally, and the superior half was snap frozen in liquid nitrogen-cooled isopentane for immunoperoxidase analyses. The inferior half was fixed in buffered formalin 10% for in situ hybridization studies.

**Reagents**

Mouse monoclonal antibodies used in this study were the following: CD4, CD8, CD11C, and HLA-DR class II (Becton Dickinson, San Jose, CA); anti-human TNF-α (Genentech, South San Francisco, CA); anti-human IFN-γ (ICN, Costa Mesa, CA); and antibovine glial fibrillary acidic protein (GFAP, Dako, Carpenteria, CA). The secondary linking reagents (biotinylated horse anti-mouse and avidin-biotin-peroxidase complex) were obtained from Vector (Burlingame, CA). The HIV probe (Dupont, Boston, MA) and in situ hybridization reagents were available commercially.

**Immunocytochemical Analysis**

The frozen tissue was cut at 5–7 μm, air dried, and fixed in reagent-grade acetone for 10 min. After drying, the slides were incubated with phosphate-buffered saline (PBS, pH 7.4) for 5 min. The tissues then were blocked with normal horse serum (20 min) and treated sequentially with the primary monoclonal antibody (30 min), the secondary biotinylated horse anti-mouse (30 min), and avidin–biotin–peroxidase complex (20 min) with 10-min PBS washes after each step. Amino-ethyl carbazole solution, which produces a red precipitate in the presence of peroxidase, was added to the slides for 10 min. They were rinsed and counterstained with Mayer’s hematoxylin for 3 min, followed by a rinse in tap water for 10 min. Subsequently, the slides were mounted in a solution of glycerol and PBS. Primary antibodies were titrated initially on known positive cell preparations. Controls for the staining procedure included both the use of an irrelevant antibody or PBS in place of the primary antibody. The frequency of positive cells was determined by counting the number of stained cells in three selected 1-mm² fields in which preliminary staining indicated leukocytic infiltrates.

**In Situ Hybridization**

The alkaline phosphatase-linked HIV-specific RNA probe used was a cocktail of three probes specific for the two GAG and one envelope regions. The procedure, as recommended by the manufacturer (Dupont), required the tissue to be rehydrated in 100 mMol/l MgCl₂ for 10 min at room temperature. Then the slides were prehybridized for 10 min at 70°C in formamide and rinsed in 5X SSC. The samples were heated to 55°C, incubated with probe solution for 60 min at 55°C, and then treated with detection buffer for 4 hr in the dark at 37°C. The development was stopped by rinsing the slides in distilled water. The slides were counterstained with either methyl green or nuclear fast red for 25 sec, rinsed with distilled water, and allowed to air dry in the dark.

**Results**

Tissues from ten HIV-seropositive patients were analyzed in this study; their clinical findings and treatments are summarized in Table 1. The retinal tissues were examined for the presence and distribution of infiltrating T-cells and macrophages using immunocytochemical methods. In three of ten retinal tissues from patients with AIDS, increased numbers (>5 cells/mm²) of T-cells were present (Table 2A). One of these retinas had retinal toxoplasmosis (from patient 2); however, the other two did not have opportunistic infection. These T-cells were localized within the nerve fiber and ganglion cell layers both in perivascular and intraparenchymal areas. Approximately equal numbers of CD4-positive (Fig. 1) and CD8-positive cells were identified. In the other seven specimens (Table 2B), no extravascular T-cells were found in the retinal tissues, and the retinal structure and cell distri-
Table 1. Clinical findings of HIV seropositive patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical ophthalmologic findings</th>
<th>Eye pathology—P.M.</th>
<th>Systemic findings, major</th>
<th>Antiviral/fungal therapy</th>
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<tr>
<td>1</td>
<td>33</td>
<td>M</td>
<td>Bilateral CMV retinitis CN VI palsy, left</td>
<td>Retinal atrophy and gliosis in posterior pole consistent with treated CMV retinitis</td>
<td>CMV encephalitis Cerebral gliosis</td>
<td>Azidothymidine Ganciclovir</td>
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<td>2</td>
<td>57</td>
<td>M</td>
<td>Not determined (terminally in hospice)</td>
<td>Retinal toxoplasmosis (Focal)</td>
<td>Primary HIV encephalitis Disseminated cryptococcosis Cerebral gliosis, perivasculitis Pneumocystis pneumonia CMV-adrenal</td>
<td>Amphotericin B Azidothymidine None</td>
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<td>3</td>
<td>43</td>
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<td>No observable pathology</td>
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<tr>
<td>4</td>
<td>58</td>
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<td>24</td>
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<td>Cryptococcal meningitis Cerebral toxoplasmosis Cerebral gliosis</td>
<td>Amphotericin B</td>
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<td>8</td>
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<td>No observable pathology</td>
<td>Pneumocystis pneumonia CMV encephalitis</td>
<td>Azidothymidine</td>
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Distribution appeared to be normal. Macrophages, identified as CD11C-positive cells, were present in all 10 affected patients, although they generally were present in greater numbers in those with T-cell infiltration (Table 2). In all instances, macrophages were localized to the nerve fiber and ganglion cell layers and were adjacent to the blood vessels (Fig. 2).

The retinas from patients with AIDS were analyzed for the presence of HIV using in situ hybridization. In four of five patients (Table 1), rare HIV-positive cells were detected in the retinal tissue (1–5 cells/mm²).

These positive cells were identified morphologically as macrophages and were located in the ganglion and inner plexiform layers (Fig. 3A). Positive cells located in the inner nuclear layer (Fig. 3B) had a morphology suggesting Müller cells.

The expression of HLA-DR class II antigen was increased in retinas of affected patients with increased leukocytic infiltration (Table 2); reactivity was localized to the nerve fiber and ganglion cell layers and around the blood vessels. Class II-positive cells appeared to be morphologically identifiable macro-

Table 2. AIDS retina tissue

<table>
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<tr>
<th>T lymphocytes</th>
<th>MØ</th>
<th>TNF-α</th>
<th>IFN-γ</th>
<th>HLA-Dr</th>
<th>HIV</th>
<th>GFAP*</th>
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<td>+</td>
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<td>+2$</td>
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<td>+1</td>
<td>-</td>
</tr>
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<td>(3)</td>
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- = no positive cell present; ± = rare positive cell (<5 cells/mm²); +1 = >5 < 20 positive cells/mm²; +2 = ≥20 positive cells/mm²; ND = not done; MØ = macrophage; TNF-α = tumor necrosis factor-alpha; IFN-γ = interferon-gamma; HLA-Dr = class II; HIV = human immunodeficiency virus; GFAP = glial fibrillary acidic protein.

* Number of plusses indicates relative intensity of staining.
† Primary HIV encephalitis with retinal toxoplasmosis.
‡ Predominant staining of astrocytes.
§ Both astrocytes and Müller cells staining.
$ Predominant staining of blood vessels.
Fig. 1. Cryostat sections of AIDS retina were examined for the presence of CD4-positive T lymphocytes. Low numbers of cells (arrows) were present perivascularly in the ganglion and nerve fiber layers (X400).

Fig. 2. Frozen sections of AIDS retina demonstrated CD11c-positive macrophages (arrows) associated with blood vessels, and in the ganglion and nerve fiber layers (X400).

Fig. 3. HIV in situ hybridization was performed on AIDS retinas. (A) HIV-positive cells were associated with perivascular macrophages (X1000). (B) Positive cells were also located in the inner nuclear cell layer (arrows) (X400).

phages, lymphocytes, and endothelial cells (Fig. 4), with focal staining consistent with astrocyte end feet. Little or no class II expression was found in most of those retinas without significant leukocytic infiltration (Table 2). Staining for GFAP revealed positive Müller cells and astrocytes in all instances; however, the intensity and extent of staining varied markedly among patients (Table 2). In control eyes and in six of seven TNF-α-negative eyes from patients, the Müller cells were positive in the inner nuclear layer, with only minimal staining of processes in the outer plexiform and outer nuclear layers. The astrocytes in the nerve fiber layer showed diffuse reactivity without identifiable processes. In the TNF-α-positive retinas from patients with AIDS, Müller cells showed more prominent GFAP reactivity extending from inner to outer limiting membranes, and thick immunoreactive astrocyte processes were found in the nerve fiber layer (Fig. 5).

Retinal tissues from the ten patients were examined for the presence of specific cytokines. We found TNF-α-positive cells localized to the nerve fiber and ganglion cell layers (Fig. 6A). There was prominent labeling of end feet adjacent to blood vessels consistent
with astroglial cell morphology (Fig. 6B). In two of four instances, these processes extended through the thickness of the retina, well into the inner nuclear and plexiform layers, indicating TNF-α reactivity in Müller cells (Fig. 6C). No TNF-α staining was detected in specimens without lymphocytic infiltration (Table 2B). No IFN-γ was detected in any of the retinal specimens tested, although activated peripheral blood leukocyte specimen control cells were IFN-γ positive.

Five neurologically normal HIV-seronegative retinas also were analyzed (Table 3). No T-cells were present in any of these five specimens, and the number of macrophages varied from none (two of five) to rare (three of five). In all instances, no TNF-α was detected. A few cells were HLA-Dr positive, but most of the reactivity was confined to endothelial cells. No HIV was detected in these tissues.

Discussion

We showed that TNF-α is present in the retinas of patients with AIDS. The presence of this cytokine is associated with infiltration of T-lymphocytes and macrophages and gliosis. Based on immunocytochemical and morphologic methods, the cellular source of TNF-α in the retina is associated with astrocytes and Müller cells. In all three TNF-α-positive cases, the population of TNF-α-positive cells had processes terminating at endothelial cells, suggesting the end-feet processes of astrocytes (Fig. 6B). In two patients (2 and 3), the population of TNF-α-reactive cells consisted of parallel elongated cells, spanning the inner retina, and suggesting Müller cell morphology (Fig. 6C). Although TNF-α originally was isolated from activated macrophages, this cytokine has been shown to be synthesized by resident cells of the CNS. Rat astrocyte cell cultures, exposed to IFN-γ, interleukin-1α, or lipopolysaccharide produced TNF-α, measured by the release of functional protein and induction of specific mRNA. Viral infections of astrocyte cultures also can induce TNF-α production.

These data suggest that, at least in vitro, astrocytes can manufacture TNF-α in the presence of immunoregulatory molecules or after direct viral infection. Studies using tissue specimens of patients with multiple sclerosis, an immune-mediated demyelinating disease with prominent leukocyte infiltration, or those with subacute sclerosing panencephalitis, a virally induced demyelinating disease, found TNF-α-positive cells with the morphologic characteristics of astrocytes. Using
Class II expression on glial cells enhances their ability to act as antigen-presenting cells and thereby mediate immune interaction with activated T-cells. The presence of HIV did not appear to correlate with either TNF-α production or class II expression because class II expression appeared to be independent of detectable virus. In addition, TNF-α induced astrocytic proliferation in several in vitro systems, including the human astrocytoma cell line U373. The strong correlation between the presence of TNF-α and retinal gliosis, as determined by the intensity and extent of staining for GFAP, suggests an altered microenvironment leading to reactive structural changes in the retina. The cytokine TNF-α can cause cytotoxicity of oligodendroglial cell cultures and degeneration of myelin sheaths, thus implying that TNF-α directly damages CNS cells. This damage may be mediated by TNF-α produced by activated leukocytes which have migrated into the CNS or by endogenously stimulated astrocytes.

The role of the T-lymphocyte in triggering TNF-α production in the retina is unclear. T-lymphocytes produce a series of cytokines, including IFN-γ (a potent inducer of TNF-α and upregulator of TNF-α receptors on target cells). However, no IFN-γ was detected in the tissue we examined, suggesting that this cytokine is not present at this stage of disease. Other studies have shown that IFN-γ can be found in the vitreous of patients with AIDS who have accompanying opportunistic infections. As the authors suggest, the source of this IFN-γ may have been the activated T-lymphocytes in the vitreous or systemic IFN-γ gaining access to the vitreous after breakdown of the blood–ocular barrier. Based on our findings, IFN-γ is not likely to be derived from retinal tissue per se. The high level of TNF-α in the three affected retinas (Table 2A) may be associated with the high numbers of macrophages present in those tissues. Not only are macrophages an important source of TNF-α, this cytokine has been shown to activate macrophages, recruit additional macrophages, and increase their cytotoxic potential. Thus, in the presence of both TNF-α and macrophages, an amplification circuit for double-staining techniques, TNF-α staining colocalized with GFAP reactivity, indicating that TNF-α was associated with astrocytes. Additional studies are needed to determine whether the astrocytes themselves produce TNF-α or bind the released TNF-α produced by activated infiltrating macrophages.

As shown in our study, the presence of TNF-α was correlated positively with increased class II expression on glial cells. This cytokine acts synergistically with IFN-γ and viral infection to induce class II expression. Class II expression on glial cells enhances their ability to act as antigen-presenting cells and thereby mediate immune interaction with activated T-cells. The presence of HIV did not appear to correlate with either TNF-α production or class II expression because class II expression appeared to be independent of detectable virus. In addition, TNF-α induced astrocytic proliferation in several in vitro systems, including the human astrocytoma cell line U373. The strong correlation between the presence of TNF-α and retinal gliosis, as determined by the intensity and extent of staining for GFAP, suggests an altered microenvironment leading to reactive structural changes in the retina. The cytokine TNF-α can cause cytotoxicity of oligodendroglial cell cultures and degeneration of myelin sheaths, thus implying that TNF-α directly damages CNS cells. This damage may be mediated by TNF-α produced by activated leukocytes which have migrated into the CNS or by endogenously stimulated astrocytes.

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**Table 3. Normal retina tissue**

<table>
<thead>
<tr>
<th>T-lymphocytes</th>
<th>MØ</th>
<th>TNF-α</th>
<th>IFN-γ</th>
<th>HLA-Dr</th>
<th>HIV</th>
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Abbreviations and symbols as in Table 2.
* Predominant staining of blood vessels.
this cytokine can be initiated. Macrophages were present in all affected retinas studied, providing a potential source of HIV-infected activated macrophages (Table 2). It has been suggested that HIV-infected macrophages may be the vehicle for HIV infection in the CNS. Therefore, HIV-infected macrophages entering the retina may be the initial source of TNF-α, which then alters the microenvironment of the retina and, ultimately, the functions of glial, neuronal, and endothelial cells.

The major pathologic process in HIV infection of the retina may not be direct HIV infection of neuronal cells because few HIV-positive cells were detected in the tissue from patients with AIDS, as shown by us and others. Furthermore, TNF-α does not appear to be acting as an amplification signal for HIV replication because the presence of HIV was independent of the absence or presence of TNF-α. The pathologic findings observed in AIDS may, however, be caused by changes in the composition of the cytokine microenvironment in the retina, thereby increasing the probability of blood vessel occlusions, cytotoxicity, and opportunistic infections. We suggest that TNF-α may play a central role in this cytokine microenvironment and be responsible in part for the initiation, progression, and dissemination of disease in the retina.

Key words: AIDS, retina, tumor necrosis factor (TNF), Müller cells, astrocytes

Acknowledgments

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References