

EXTENDED REPORT

Human retinal microglia express candidate receptors for HIV-1 infection

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9 October 2004**Background/aims:** Microglia are the primary antigen presenting cells in the central nervous system and the retina, and can harbour viral antigens that may damage neural tissue via the release of neurotoxins. All cells bearing CD4 molecules and co-receptors (members of the chemokine receptor and Fc γ receptor families) are potential targets for the human immunodeficiency virus (HIV). In this study, retinal microglia (in vitro and in situ) were investigated for the expression of candidate HIV-1 binding receptors.**Methods:** Cultured human retinal microglia and frozen sections of human retinas were used. Immunohistochemistry was used to investigate expression of cell surface receptors necessary for HIV-1 infection: CD4, CC chemokine receptor 5 (CCR5), and Fc γ receptors.**Results:** Human retinal microglia expressed detectable levels of CD4, CD16, CD64, and CCR5 in vitro and Fc γ receptor I (CD64) in situ.**Conclusions:** Human retinal microglia express several candidate receptors required for viral binding and as such may be a potential reservoir for HIV-1 infection.

Microglia constitute a distinct cell population within the central nervous system (CNS) including the retina, and are involved in several physiological¹ as well as pathological processes.² The phenotype of microglia has been demonstrated to be consistent with that of myeloid cells.^{3–4} During acquired immunodeficiency syndrome (AIDS), microglial cells are infected by human immunodeficiency virus-1 (HIV-1), contributing to neuronal damage and blood-brain barrier (BBB) breakdown through their activation and eventual secretion of potential neurotoxins.^{5–6} In vitro studies have demonstrated that microglia can be directly infected.⁷ In vivo, HIV-1 can infect endothelial cells and gain access to the brain tissue across the BBB.⁸ Moreover, HIV-1 can be “hidden” in blood borne monocytic cells and carried into the brain tissue during the turnover of monocytes with the local microglial cells, evading immune surveillance in accordance with the “Trojan horse” theory.⁹

Clinical studies have shown that HIV-1 infected individuals can suffer visual field disturbances,¹⁰ impairments in colour vision,¹¹ and opportunistic retinitis.¹² The underlying pathogenesis of these ocular changes, including the involvement of retinal microglia, remains to be determined; however, retinal glial cells, including microglia, have been reported as candidates for HIV-1 infection,¹³ and viral particles have been found within human retinas.¹⁴

Several pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF- α), interleukins IL-1, and IL-6 have been demonstrated in HIV-1 infected retina,¹⁵ perhaps derived from activated microglia, an important source of pro-inflammatory cytokines in other neural tissues.^{16–17} The release of pro-inflammatory cytokines has also been implicated in the induction of ganglion cell loss¹⁸ and breakdown of the blood-retinal barrier (BRB).¹⁹ The latter can contribute to the pathogenesis of cystoid macular oedema²⁰ and could eventually provide access to opportunistic infectious agents such as cytomegalovirus (CMV) that are commonly seen in HIV-1 patients.²¹

The potential infectivity of retinal microglia by HIV-1 remains to be confirmed. In vivo viral antigen immunoreactivity has not been conclusively shown, and ultrastructural studies have been unable to convincingly demonstrate

HIV-1 infected retinal microglial cells. In this study, we investigated cultured and in situ human retinal microglia for the expression of surface receptors considered important for cellular entry of HIV-1.

MATERIALS AND METHODS

Microglial culture

For tissue culture, adult human eyes from donors aged 10–39 years ($n = 7$), with 17 (SD 5.5) hours postmortem delay and free from detectable ocular history, were obtained from the Lions NSW Eye Bank and with approval from the human ethics committee, University of Sydney. All studies conformed to the tenets of the Declaration of Helsinki.

Human retinal microglia were cultured as described previously.²² Briefly, the retina was dissected from the choroid and the retinal pigmented epithelium (RPE), then incubated in 0.05% trypsin/0.02% EDTA (ThermoElectron Pty Ltd, Australia) and 150 μ l of DNase (Roche Applied Sciences Australia Pty Ltd) for 10 minutes at 37°C. Digests were doubled filtered through 70 μ m and 44 μ m meshes, centrifuged, and the cells resuspended in growth medium (Iscoves Modification of Dubecco's medium, IMDM, ThermoElectron) supplemented with 10% FBS, 50 IU/ml penicillin, 50 μ g/ml streptomycin, and 2 mM glutamine, and cultured in a humidified atmosphere of 5% CO₂ and air at 37°C. After 7 days, cultures were washed with HBSS and fresh growth medium was added and cells were cultured for a further 7 days. The supernatant containing predominantly microglia²² was centrifuged at 400 \times g for 7 minutes at room temperature (RT). The pellet was then resuspended in growth medium, and cells seeded on plastic and glass coverslips for immunostaining experiments.

Abbreviations: AIDS, acquired immunodeficiency syndrome; BBB, blood-brain barrier; BRB, blood-retinal barrier; CCR5, CC chemokine receptor 5; CMV, cytomegalovirus; HIV, human immunodeficiency virus; IL, interleukin; INL, inner nuclear layer; IPL, inner plexiform layer; PBS, phosphate buffered saline; RPE, retinal pigmented epithelium; TNF- α , tumour necrosis factor alpha

Immunohistochemistry: fluorescence

After 3–5 days in culture, coverslips were fixed in 2% paraformaldehyde, and subsequently rinsed in 0.1 M phosphate buffered saline (PBS). Following incubation in 10% normal sheep serum (NSS) for 15 minutes to reduce non-specific antibody binding, cells were immunolabelled with primary mouse monoclonal antibodies to CD4 (Neomarkers, 1:50), CD16, CD32, CD64, CD45, and CCR5 (Becton-Dickinson Pty Ltd, 1:50) for 1 hour at RT. After rinsing in PBS, coverslips were incubated in biotinylated sheep anti-mouse immunoglobulins (Amersham Pharmacia Biotech Pty Ltd, 1:100) for 1 hour, further rinsed in PBS, and incubated in streptavidin-Cy3 (Zymed Inc, San Francisco, CA, USA) (1:200) for 45 minutes, followed by three washes in PBS. All antibodies were diluted in PBS and 2% NSS. Immunolabelled coverslips were mounted onto glass slides with glycerol.

Immunohistochemistry: immunoperoxidase

After blocking in 10% NSS and incubating in primary and biotinylated secondary antibodies, coverslips were incubated in ExtrAvidin peroxidase (Sigma Pty Ltd) (1:200 in PBS) for 1 hour and antibody binding visualised with 3-3' diaminobenzidine (DAB) (Sigma). Coverslips were rinsed several times in PBS, counterstained in haematoxylin for 2–3 minutes and dehydrated through alcohols and xylene and mounted in DePeX.

Human retinal sections

Adult human eyes from donors aged 35–70 years ($n = 7$), less than 24 hours postmortem delay and free from detectable ocular history, were obtained with consent from the Lions NSW Eye Bank and approval from the human ethics committee, University of Sydney. The anterior segments and vitreous were removed and the eye cups fixed in 2% paraformaldehyde/PBS for more than 24 hours. Retinal trephines (6 mm diameter), centred approximately 3 mm from the papillomacular region, were taken from fixed eye cups. Retinas were detached in PBS and residual vitreous gently removed from the retinal surface with sponge and scissors, followed by several rinses in PBS. Specimens were then incubated in a 30% sucrose/PBS solution for 1 hour at RT. Following this, the tissues were embedded in TissueTek (Sakura Finetek, USA), frozen in liquid nitrogen cooled isopentane and 15 μ m sections cut using a Leitz Cryostat. The sections were collected on polylysine and gelatin coated glass slides and kept at -20°C until used.

Immunohistochemistry

After rinsing in several changes of PBS for 15 minutes, sections were incubated in 10% NSS for 30 minutes at RT to reduce non-specific binding. Primary antibodies were then applied as above, and after an overnight incubation at 4°C , slides were rinsed three times in PBS over 15 minutes. Localisation of the primary antibodies was detected using a biotinylated secondary anti-mouse antibody, ExtrAvidin peroxidase, and DAB as described above (immunocytochemistry: peroxidase). The slides were washed, counterstained with haematoxylin, dehydrated, coverslipped with DePeX and examined with light microscopy.

RESULTS

Microglia in culture

Within 3–5 days of seeding, three separate microglial cultures grew on coverslips. Cultured retinal microglia displayed an opalescent colour and veiled cell morphology, and remained adherent to the coverslips, helping to isolate them from the mixed retinal glial cells. All immunolabelling experiments were done after 14 days' culture, yielding increased numbers of resting microglial cells with typical ramified morphology.

CD4 expression

In culture, ramified retinal microglia expressed detectable levels of CD4 immunostaining. Immunoperoxidase positive granules were localised within the cell bodies while the cell processes stained weakly (fig 1B and C, table 1). IgG non-specific isotype controls were negative (fig 1A, 2A) and CD45 immunolabelled positive controls showed strong staining of microglia (fig 1D, 2B). No obvious CD4 immunoreactivity was observed in any of the sections from human retinas (not shown).

CCR5 expression

Cultured retinal microglia expressed CCR5 receptors (fig 2C and D, table 1). Microglial cells with bipolar or ramified morphology were selected for microscopic examination. Bipolar ramified microglia displayed dense staining of the cell body but not the processes, in contrast with CD45 immunostaining where both cell bodies and processes were visible (fig 2B). Overall, fewer CCR5 positive cells were observed compared to CD45 positive cells in microglial culture. CCR5 immunoreactivity could not be detected in sections from human adult retinas (not shown).

Fc γ receptor expression

In culture, retinal microglia expressed immunoreactivity for Fc γ receptor III (CD16) (fig 2E) and Fc γ receptor I (CD64) (fig 2F). Retinal sections from all specimens showed microglial cells immunostained for anti-Fc γ receptor I (CD64) antibody (fig 3C). The CD64 immunoreactive cells displayed different morphologies depending on their location within the retinal layers, similar to the patterns of CD45 immunostaining of microglia (fig 3B). Microglial cells in the nerve fibre layer displayed an elongated shape, while microglial cells in the inner plexiform layer (IPL) and the inner nuclear layer (INL) had highly branched dendritiform morphology, although less ramified in the INL (fig 3C, table 1). Vessel associated microglia were CD45 and CD64 immunoreactive. IgG non-specific isotype controls were negative (fig 3A), and no obvious immunostaining was seen for antibodies to Fc γ receptors II or III (CD32 or CD16 respectively) (not shown).

DISCUSSION

Infection of monocytes/macrophages with HIV-1 occurs through direct interaction of the viral envelope glycoprotein gp120 with the CD4 receptor.²³ The lack of evidence confirming expression of this surface marker on certain cell types including microglia and astrocytes has prompted research into CD4 independent binding sites. Several earlier studies have suggested that viral infection may also occur

Table 1 Expression of immunoreactivity for viral binding receptors on cultured and in situ human retinal microglia

	CD4	CD16 (Fc γ RIII)	CD32 (Fc γ RII)	CD64 (Fc γ RI)	CD45	CCR5
Cultured microglia	+	+	-	+	+	+
In situ microglia	-	-	-	+	+	-

+ detected; - not detected.

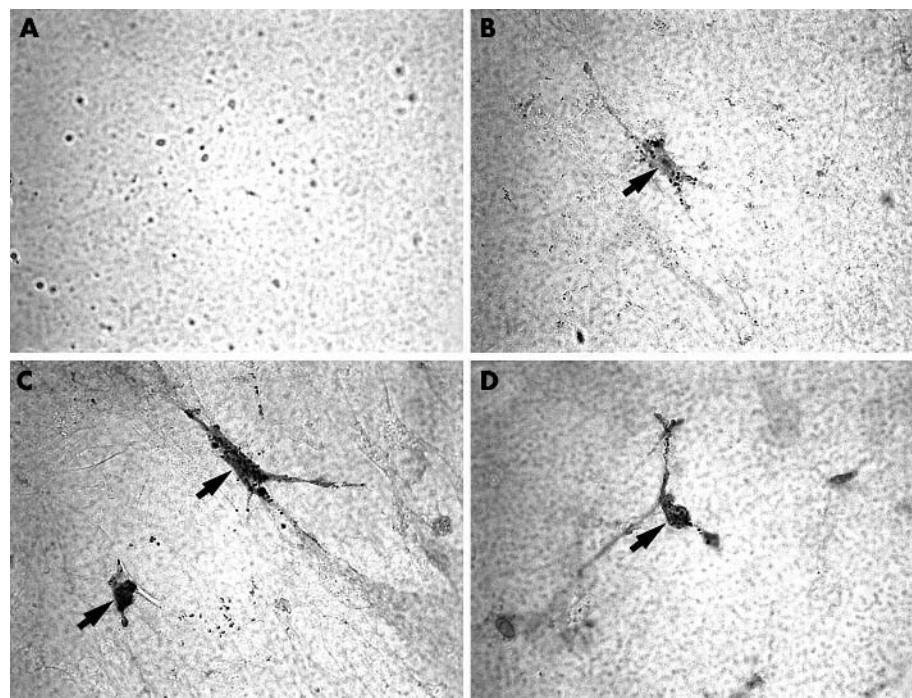


Figure 1 Immunoperoxidase staining of cultured human microglia. (A) IgG non-specific isotype control; (B and C) microglial cells (arrows) showing CD4 immunoreactivity; (D) a CD45 immunoreactive microglial cell (arrow). ($\times 50$.)

through the interaction of antibody opsonised HIV-1 with the Fc γ Rs on mononuclear phagocyte series cells²⁴ or through chemokine receptor molecules.²⁵ More recently, the presence of CD4 has been shown to be essential for viral binding.²⁶ Additionally, chemokine receptors—that is, CCR3, CXCR4, and CCR5, function as co-receptors necessary for viral internalisation²⁶ and Fc γ Rs enhance viral stability at the cell

surface, allowing infectivity through high affinity CD4 interactions.²⁷

Microglia and CD4 expression

CD4 normally has an important role in activating T lymphocytes by interacting with major histocompatibility complex class II (MHC-II) molecules on the surface of local macrophages during antigen presentation to T cells.²⁸ During HIV-1 infection, the presence of CD4 is crucial for the efficient binding of virions to the plasma membrane.²⁶

CD4 has been found to be highly expressed on Langerhans cells,²⁹ U937 monocytic cells,³⁰ mouse brain microglia³¹ and more recently on resting human retinal microglia.³² However, many studies have been unable to detect CD4 on human brain microglia³³ or have observed only very low CD4 levels in situ on activated human brain microglia.³⁴

In the present study, we were unable to detect CD4 immunoreactivity on human retinal sections. In contrast, cultured retinal microglia expressed detectable levels of CD4 and this may be related to activation of microglia in culture or isolation of microglia from the normal immunosuppressive retinal environment.^{32 35}

Microglia and Fc receptor (FcR) expression

In this study, we have shown that cultured retinal microglial cells expressed Fc γ RI (CD64) and Fc γ RIII (CD16). In situ microglial cells expressed Fc γ RI (CD64) but not Fc γ RII (CD32) or Fc γ RIII (CD16) in normal retina. The presence of Fc γ receptors—that is, Fc γ RI (CD64), Fc γ RII (CD32), and Fc γ RIII (CD16) on human microglia has been reported in brain tissues from patients with multiple sclerosis.³⁶

Fc γ R expression primarily serves to trigger the lysis of extracellular antibody coated targets.³⁷ However, some pathogens may exploit the process of Fc γ R binding to facilitate penetration into Fc γ R expressing cells.³⁸ Fc γ RIII has been reported to be absent on U937 cells³⁹ and in such cells, CD4 in addition to Fc γ I and Fc γ II receptors has been demonstrated to be necessary for any infection via the antibody dependent enhancement (ADE) process.⁴⁰

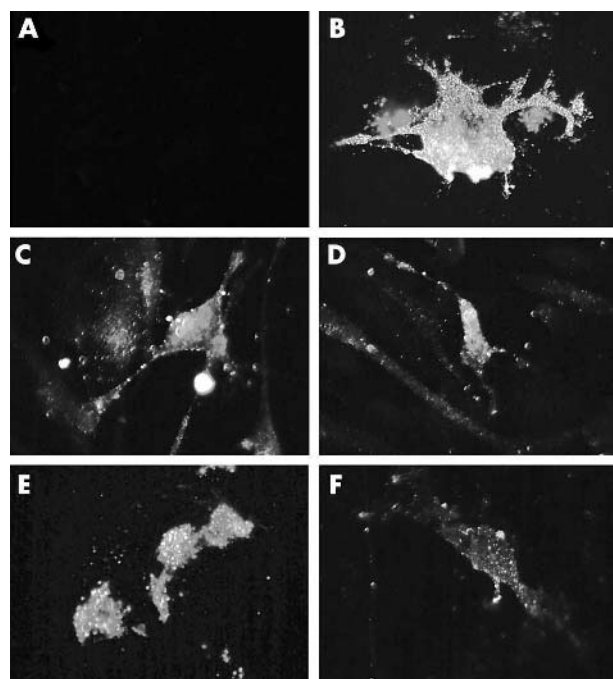


Figure 2 Immunofluorescence staining of cultured human microglia. (A) IgG non-specific isotype control; (B) a CD45 immunoreactive microglial cell; (C and D) microglial cells showing CCR5 immunoreactivity; (E) CD16 immunoreactive microglial cells; (F) a CD64 immunoreactive microglial cell. ($\times 50$.)

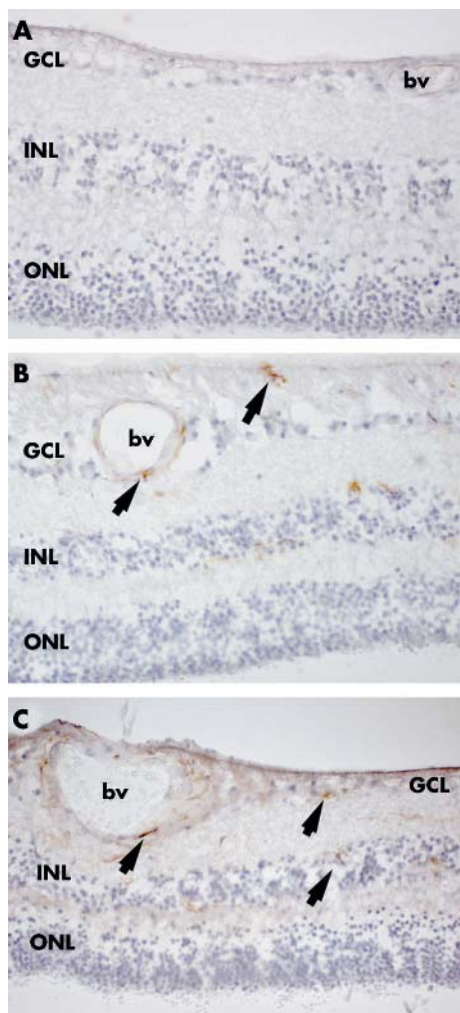


Figure 3 Immunoperoxidase staining of human retinal sections. (A) IgG non-specific isotype control ($\times 50$); (B) vessel associated and parenchymal microglial cells immunolabelled with anti-CD45 antibody (arrows) ($\times 50$); (C) CD64 immunopositive vessel associated and parenchymal cells are seen in the inner retinal layers (arrows) ($\times 50$). (GCL, ganglion cell layer; INL, inner nuclear layer; ONL, outer nuclear layer; bv, blood vessel)

Although infection with HIV-1 in monocytes/macrophages can occur via interaction of the viral envelope glycoprotein (gp120) with the CD4 receptor,⁴¹ viral infection may also occur through the interaction of antibody opsonised HIV-1 with Fc γ receptors on monocytic cell types in an ADE process.⁴² The involvement of Fc γ receptors in HIV membrane fusion remains to be defined. One study, for example, found that during infection via the Fc γ R pathway, high affinity Fc γ RI (CD64) as well as Fc γ RIII (CD16) may be critical for ADE to occur.²⁵ In contrast, another study has shown that macrophages expressing all three Fc γ receptors, only antibodies against Fc γ RIII molecules (CD16) completely abolish viral penetration.⁴³ HIV-1 infection of cells that do not express Fc γ RIII appears to be dependent on the presence of gp120-CD4 binding.⁴⁴

Microglia and chemokine receptor expression

Individuals homozygous to mutant alleles of CCR5 with a 32 bp deletion ($\Delta 32$) have been shown to be resistant to HIV-1 infection, indicating the importance of CC chemokine receptor CCR5 during HIV-1 infection.⁴⁵ Recent studies have demonstrated that gp120-chemokine receptor interaction

occurs at the level of the third variable loop, more precisely next to the CD4 inducible epitopes on gp120.⁴⁶ The presence of soluble CD4 and preservation of the third loop are critical for viral binding to CCR5.⁴⁷ Deletion of this loop preserves binding of CD4 to gp120 but ablates binding to CCR5, although the deletion of both first and second loops does not alter the binding of gp120/CD4 complex to CCR5.⁴⁸ Moreover, the addition of gp120 from macrophage but not T cell tropic isolates may inhibit the binding of chemokines to CD4 and CCR5 expressing cells.⁴⁹ In situ, CD4 is more important for the interaction between viral envelope and the chemokine receptors and the addition of soluble CD4 can abolish HIV-1 infection.⁴⁸

The expression of chemokine receptors has not been reported previously on human retinal microglia. However, U937 monocytic cells and human brain microglia have been shown to express CCR5, the co-receptor most commonly used by viral isolates; these cells can be infected with many macrophage tropic HIV-1 strains.⁵⁰ Moreover, antibodies against CCR5 can inhibit microglial infection with HIV-1, while anti-CCR3 and anti-CXCR4 antibodies have little or no effect.⁵¹

The present study shows that retinal microglia can express immunoreactivity for viral binding receptors and as such, may be involved in the pathogenesis of viral retinopathies including HIV-1/AIDS retinopathy.

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