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Interleukin-8 Receptor B Immunoreactivity in Brain and Neuritic Plaques of Alzheimer's Disease

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Cytokines mediate inflammatory responses through their receptors in the hematopoietic system. In a search for potential mediators of inflammatory responses in Alzheimer's disease, we examined brain for cytokine receptors. Herein we describe interleukin-8 receptor B (IL-8RB, also termed CXCR2) immunoreactivity in the central nervous system. Strong IL-8RB immunoreactivity is present in both Alzheimer's disease and control brains. Neurons, dendrites, and axons are clearly immunoreactive. In Alzheimer's disease, IL-8RB immunoreactivity is also present in some swollen dystrophic neurites of neuritic plaques. Double staining and confocal microscopic analysis reveals that these IL-8RB-positive neurites in plaques are neurofilament positive and are distinct from astrocytic or microglial processes. In general, these IL-8RB-positive neurites do not co-localize with PHF-1 or AT8 (hyperphosphorylated tau) immunoreactive neurites but instead co-localize with βPP-positive neurites. These results demonstrate for the first time IL-8RB immunoreactivity in the central nervous system and imply a new role for this receptor outside the hematopoietic system. The strong presence of IL-8RB on neurons and the potential of glial cells to produce IL-8 suggest that this system might mediate neuronal-glial interactions. (Am J Pathol 1997, 150:1267–1274)

A number of inflammatory proteins such as interleukin (IL)-1α, IL-1β, IL-6, tumor necrosis factor-α, complement, acute phase proteins, proteases, and protease inhibitors have been found to be associated with amyloid plaques of Alzheimer's disease (AD).[1–4] These molecules may well mediate complex cellular interactions. For example, both IL-1β and tumor necrosis factor-α have been shown to stimulate cultured normal human astrocytes to secrete IL-8.[5] Others have also reported the ability of cultured astrocytes and glioblastoma to produce IL-8.[6,7] IL-8 was shown to prolong the survival of rat embryonic hippocampal neuronal culture.[8] Most recently, it was demonstrated that amyloid-β (Aβ) can stimulate cultured astrocytes to express IL-8, and this effect was particularly marked in the presence of IL-1β.[9]

Because IL-8 is a member of the chemoattractant cytokine (chemokine) family,[10] its expression by astrocytes and its potential role in brain are of interest. However, there has been no report of IL-8 receptors in brain. IL-8 is known to have two receptors, receptor A (IL-8RA) and receptor B (IL-8RB), which are also termed CXC chemokine receptor 1 (CXCR1) and 2 (CXCR2) respectively. Both receptors are G-protein-coupled membrane molecules, and they share a 74% homology at the protein level. They are present on neutrophils, monocytes, and a subset of T lymphocytes.[11,12] IL-8RB has also been found on endothelial cells and keratinocytes.[13] IL-8RA has only IL-8 as a ligand; IL-8RB has not only IL-8 but also GROα, NAP2, and ENA78 as ligands. Both IL-8RA and IL-8RB can mediate neutrophil chemotaxis and activation (ie, degranulation and up-regulation of integrins). In addition, IL-8RB has also been implicated in angiogenesis and cutaneous burn wound repair.[13,14] We therefore examined brain for the presence of IL-8 and both of its receptors.

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Materials and Methods

Monoclonal Antibodies (MAbs)

MAb 2A2 (IgG1) specific for IL-8, 5A12 (IgG2b) and 7D9 (IgG1) specific for IL-8RA, and 6C6 (IgG1), 4A4 (IgG1), and 7E11 (IgG1) specific for IL-8RB were made by LeukoSite. The IL-8RA and IL-8RB antibodies were made by immunizing mice using IL-8RA and IL-8RB transfectants, respectively.[12] The two IL-8RA antibodies were found to be specific to the amino-terminal region of the receptor; all IL-8RB antibodies were found to be specific to a similar amino-terminal region of the molecule.[15] The IL-8RB antibody 6C6 has also been tested on IL-8RB-transfected mouse L1–2 cell lysate by Western blotting. In the IL-8RB transfectant, 6C6 antibody recognized the approximately 40-kd full-length and 35-kd de-*N*-glycosylated form of the receptor (S. X. Qin, unpublished data); In transfectant with the vector alone, there were no 6C6 immunoreactive bands. In both AD and control brain homogenates, using the 6C6 antibody, we have observed the 35-kd and an 18-kd band (possibly a breakdown product).

To confirm the pattern of immunostaining, two additional IL-8RB antibodies, 10H2 (ATCC HB-11494) and 4D1 (ATCC HB-11495),[11] were also used. The specificity of these two antibodies has also been mapped to the amino-terminal region of the receptor.[15]

Antibody 10D5 (specific for Aβ) and antibodies to different regions of βPP (1G5, anti-βPP; 7H5, anti-KPI) were from Athena Neurosciences (South San Francisco, CA).[16] PHF-1 (specific for phosphorylated tau) was courtesy of Dr. Peter Davies,[17] and AT-8 (specific for phosphorylated tau)[18] was from Biosource International, Camarillo, CA. Antibodies to glial fibrillary acidic protein and to neurofilament heavy chain were from Sigma Chemical Co., St. Louis, MO, and LN3 (specific for major histocompatibility (MHC) class II) was from ICN Chemicals, Irvine, CA. MAbs were either purified and used at a concentration of 5 to 10 μg/ml or hybridoma supernatants and used 1:1 to 1:3 diluted.

Tissue Preparation

Postmortem brain tissue was taken from the temporal lobes of 12 AD and 11 control patients (ranging from 42 to 100 years of age). The diagnosis of AD and control was made by the Massachusetts Alzheimer Disease Research Center brain bank (Dr. E. T. Hedley-Whyte, Director) using Khachaturian criteria[19] applied to Bielschowsky staining of paraffin-embedded blocks. All brains were processed within 24 hours of death (ranging from 5 to 24 hours; average, 14 hours). Fresh tissue blocks containing the hippocampal formation, parahippocampal gyrus, and adjacent temporal neocortex were immersion fixed in periodate-lysine-paraformaldehyde for 48 hours and then transferred to 15% glycerol in sterile 0.1 mol/L phosphate-buffered saline (PBS), pH 7.4, for approximately 24 hours. The 50-μm-thick sections were cut with a sledge freezing microtome. The sections were stored in 15% glycerol PBS solution at −20°C until use.

Immunohistochemistry

Immunohistochemistry was carried out on free-floating sections. After a brief rinse in 0.05 mol/L Tris buffered saline (TBS), pH 7.4, sections were permeabilized and endogenous peroxidase quenched with 0.5% Triton X-100 in 3% hydrogen peroxide for 20 minutes. They were then blocked with 3% nonfat dry milk in TBS at room temperature (RT) for 1 hour. MAbs were used as primary antibodies (diluted in 1.5% normal goat serum) for immunostaining at 4°C overnight. Tissues were then stained with a secondary antibody, horseradish-peroxidase-conjugated goat anti-mouse Ig (Jackson ImmunoResearch Laboratories, West Grove, PA) at a 1:200 dilution for 1 hour at RT. 3′,3′-Diaminobenzidine (Sigma) was used as the chromogen.

For double staining, tissue sections were permeabilized with 0.5% Triton X-100 and blocked in 3% normal goat serum TBS for 1 hour at RT. Staining with first primary antibodies in 1.5% normal goat serum TBS were carried out at 4°C overnight. Bodipy Fluorescein goat anti-mouse Ig (Molecular Probes, Eugene, OR) at 1:20 to 1:200 in 1.5% normal goat serum TBS was used as the secondary antibody at RT for 1 hour. Sections were rinsed and then blocked in 1.5% normal goat serum, 1.5% normal mouse serum TBS at RT for 1 hour. Biotinylated IL-8RB antibody (6C6, 5 μg/ml) in the above blocking buffer was used for another overnight staining at 4°C. Cy3 streptavidin (Jackson ImmunoResearch) at a 1:750 dilution in TBS was added for another 1-hour staining at RT. Between each step, sections were washed three times in TBS (5 minutes each). All procedures were carried out with gentle shaking. Both diaminobenzidine-developed and fluorescent-stained sections were mounted and air dried. Sections were dehydrated and coverslipped in Permount (Sigma).

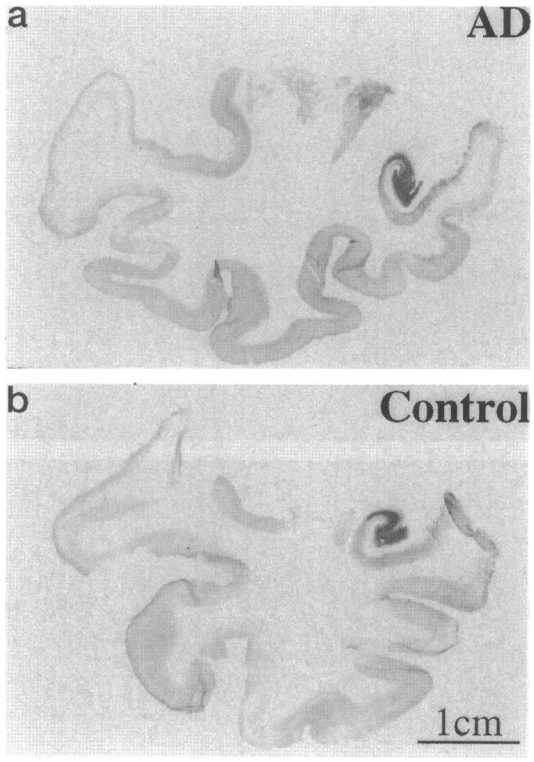

Figure 1. *Low-power view of IL-8RB (MAb 6C6) immunoreactivity in a 74-year-old male patient with AD for 11 years* (a) *and a 100-year-old female control patient* (b). *A similar pattern of immunostaining can be seen in all cases, with the strongest IL-8RB staining in the hippocampal formation.*

Confocal Microscopic Analysis

Fluorescent immunostained sections were analyzed on a BioRad MRC1024 confocal microscope with a krypton/argon laser. For Bodipy FL, the excitation filter was 488 nm and the emission filter was 522 nm. For Cy3, excitation and emission filters were 568 and 605 nm, respectively.

Results

IL-8RB immunoreactivity was quite strong and was present in the hippocampal formation of both AD and the control tissues with all of the IL-8RB antibodies. Staining by 6C6 and 4A4 were stronger than that by 7E11. However, the patterns of staining by all three antibodies were similar. Figure 1 shows a low-power view of IL-8RB (6C6) staining of AD and control brains. Two additional IL-8RB antibodies, 10H2 and 4D1, produced by a different laboratory[11] showed a similar pattern of immunoreactivity although weaker than the staining by 6C6 and 4A4. Additional AD and control cases were further examined (12 AD and 11 control cases in total) using one of the IL-8RB antibodies, 6C6. Despite case to case variation in the intensity of staining, they all showed a similar pattern of immunoreactivity in the hippocampal formation (Figure 1).

Analysis of the IL-8RB immunoreactive areas in the hippocampal formation of both AD and control brains revealed abundant but diffuse staining of dentate gyrus, CA4, CA3, and CA1. The intensity of staining was in the following order: dentate gyrus and CA4 > CA3 > CA1 > subiculum ≥ entorhinal cortex. In the dentate gyrus, the inner one-third of the molecular layer and the granular and polymorphic layers were all IL-8RB positive (Figure 2a). Pyramidal neurons, proximal axons, and dendrites in CA regions, particularly in CA1 of control brains, were clearly immunoreactive (Figure 2, b and c). Frequently, immunostaining of punctate morphology could be seen representing axons (Figure 2d).

Gray matter in temporal neocortex, visual cortex, striatum, and the amygdala were also IL-8RB immunoreactive but to a lesser extent compared with the staining in the hippocampal formation (Figure 3). IL-8RB immunostaining in the gray matter was diffuse in the neuropil. Nevertheless, some individual neurons (mostly large pyramidal neurons) and their processes could be discerned. Staining of the cerebellum also showed a distinct pattern of IL-8RB reactivity (Figure 3). The strongest staining was clearly confined to the granular layer.

IL-8RB-Positive Neuritic Plaques in AD

In AD brains, IL-8RB immunoreactivity was also present in the dystrophic neurites of some neuritic plaques (Figure 4). The neurites frequently were swollen with marked varicosities. Less than 50% of amyloid plaques were IL-8RB-positive plaques. Generally, there were more IL-8RB-positive plaques in the hippocampal formation and amygdala than in any other regions of the brain. There was a great deal of case to case variation in the number of IL-8RB-positive plaques. The number of IL-8RB-positive plaques did not appear to correlate with duration of dementia in cases varying from 1 to 16 years. In certain control cases, occasional IL-8RB-positive neuritic plaques were also present.

Double Staining and Confocal Microscopic Studies of IL-8RB-Positive Neuritic Plaques

Double staining of IL-8RB *versus* Aβ staining showed that IL-8RB-positive neurites were intertwined within and around the amyloid deposit (Figure 5, a and b). All IL-8RB-positive plaques had Aβ

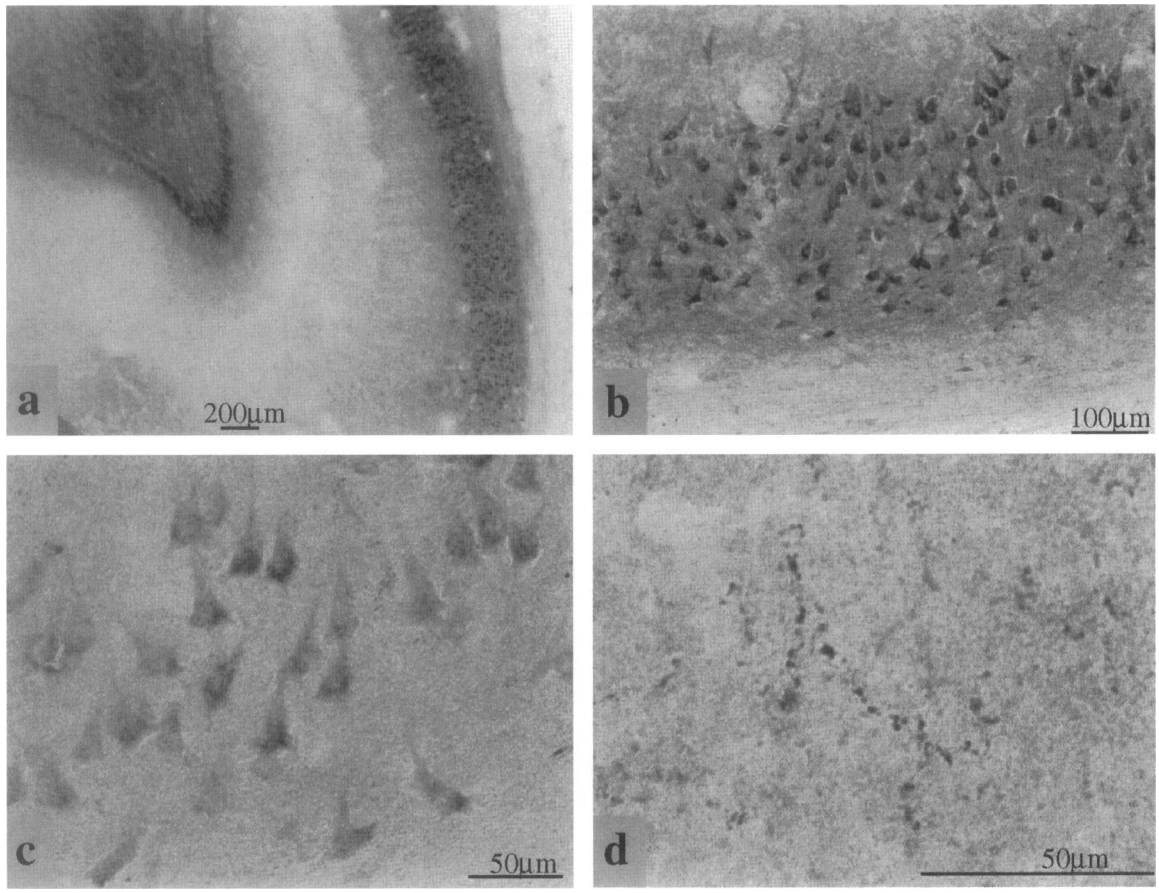

Figure 2. *IL-8RB (MAb 6C6) immunoreactivity in the hippocampal formation of a 66-year-old male control patient.* a: *The dentate gyrus and CA regions are strongly immunoreactive.* b: *Pyramidal neurons in CA1 region are clearly immunostained,* c: *At high magnification, cell body, dendrites, and axons of the pyramidal neurons can be seen clearly immunostained.* d: *Punctate staining of neuronal processes can be seen frequently.*

deposition. For IL-8RB staining *versus* PHF-1 or AT8 (hyperphosphorylated tau) staining, we found that the IL-8RB-positive neurites rarely co-localized with PHF-1 or AT8 immunoreactive neurites, and PHF-1 or AT8 immunoreactive neurons (ie, NFT) were rarely IL-8RB positive (Figure 5c). Interestingly, IL-8RB *versus* βPP staining (1G5 for βPP) showed that almost all IL-8RB-positive neurites were positive for βPP staining and *vice versa*; the pattern of double staining with the βPP-KPI domain (7H5) was similar to that with βPP (Figure 5d). Staining of IL-8RB *versus* glial fibrillary acidic protein (for astrocytes) and MHC class II (for microglia) showed a strong astrocytic and microglial presence closely associated with IL-8RB-positive plaques (Figure 5, e and f), but astrocytes and microglia did not contribute to any of the IL-8RB-positive processes. By contrast, neurofilament staining did co-localize with both IL-8RB-positive cell bodies and dystrophic neurites, suggesting their neuronal origin (data not shown).

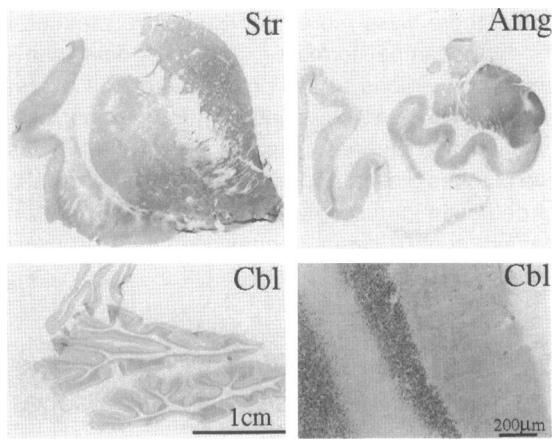

Figure 3. *Low-power view of IL-8RB (MAb 6C6) immunoreactivity in other cortical and subcortical regions. Gray matter of striatum (str), amygdala (Amg), and cerebellum (Cbl) are all IL-8RB positive. The scale bar is the same for all three regions. At higher magnification, granular cells in cerebellum are shown to be clearly immunostained.*

Immunostaining for IL-8RA (antibodies 5A12 and 7D9) and IL-8 (antibody 2A2) were negative, although those antibodies are known to immunostain other tissues such as skin and nasal polyps using similar fixation methods (D. Ringler, unpublished

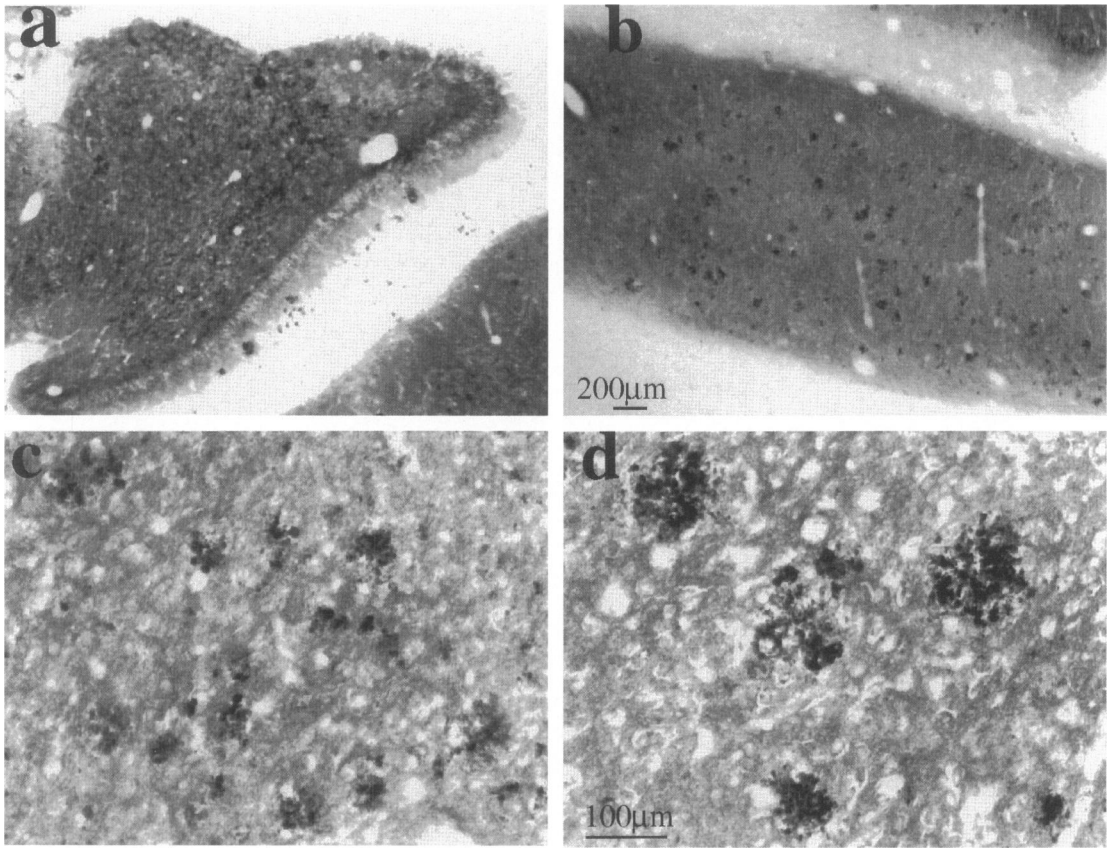

Figure 4. *IL-8RB (MAb 6C6) immunoreactivity in the hippocampal formation and plaques in an AD patient (the same case as Figure 1a). At lower magnification, IL-8RB staining is shown in dentate gyrus* (**a**) *and CA1 region* (**b**). *At higher magnification, the IL-8RB-positive plaques are shown in two different fields of CA1 region* (**c** *and* **d**).

data). It is possible that this reflects sensitivity issues if they are expressed in relatively low amount or are degraded during the postmortem period.

Discussion

Recent evidence suggests that Aβ participates in a complex inflammatory response in brain.[1–4] *In vitro*, Aβ has been shown to stimulate astrocytes to secrete cytokines such as IL-1 and IL-8,[9] and Aβ can also stimulate free radical production.[20–21] Recently, it was shown that reactive oxygen and reactive nitrogen intermediates may in turn stimulate cells to synthesize IL-8.[22] Other toxic stimulants may also have the potential to stimulate astrocytes or microglia to secrete cytokines, such as IL-8 or other potential IL-8RB ligands. Whether or not these observations impact the pathophysiology of AD depends to a great extent on whether they occur *in vivo* and what biological responses to cytokines occur in the central nervous system (CNS). As a first step in understanding these processes, we have explored the expression of IL-8 and its receptors in the CNS.

We find robust expression of IL-8RB in brain. Neurons are the primary cell type expressing IL-8RB in normal brain, implying a previously unsuspected role in normal neuronal physiology. Moreover, dystrophic neurites that are associated with a subset of senile plaques are strongly IL-8RB positive. Interestingly, those neurites co-localize with βPP-positive but not with PHF-positive neurites.

The exact role of IL-8RB in the brain is unknown. In the periphery, IL-8RA and IL-8RB on neutrophils are functionally different, probably through different signaling pathways. Several responses such as cytosolic Ca^{2+} increase and the release of granule enzymes as well as chemotaxis are induced by both receptors, whereas the respiratory burst and the activation of phospholipase D are exclusively mediated through IL-8RA.[23] Antibodies used in our study (5A12, anti-IL-8RA; 6C6, anti-IL-8RB) inhibit the above responses through their respective receptors. In addition, IL-8RB has also been implicated in angiogenesis and cutaneous wound repair.[13–14] Therefore, the role of IL-8RB in the periphery seems to be physiological and may also be associated with promoting growth.

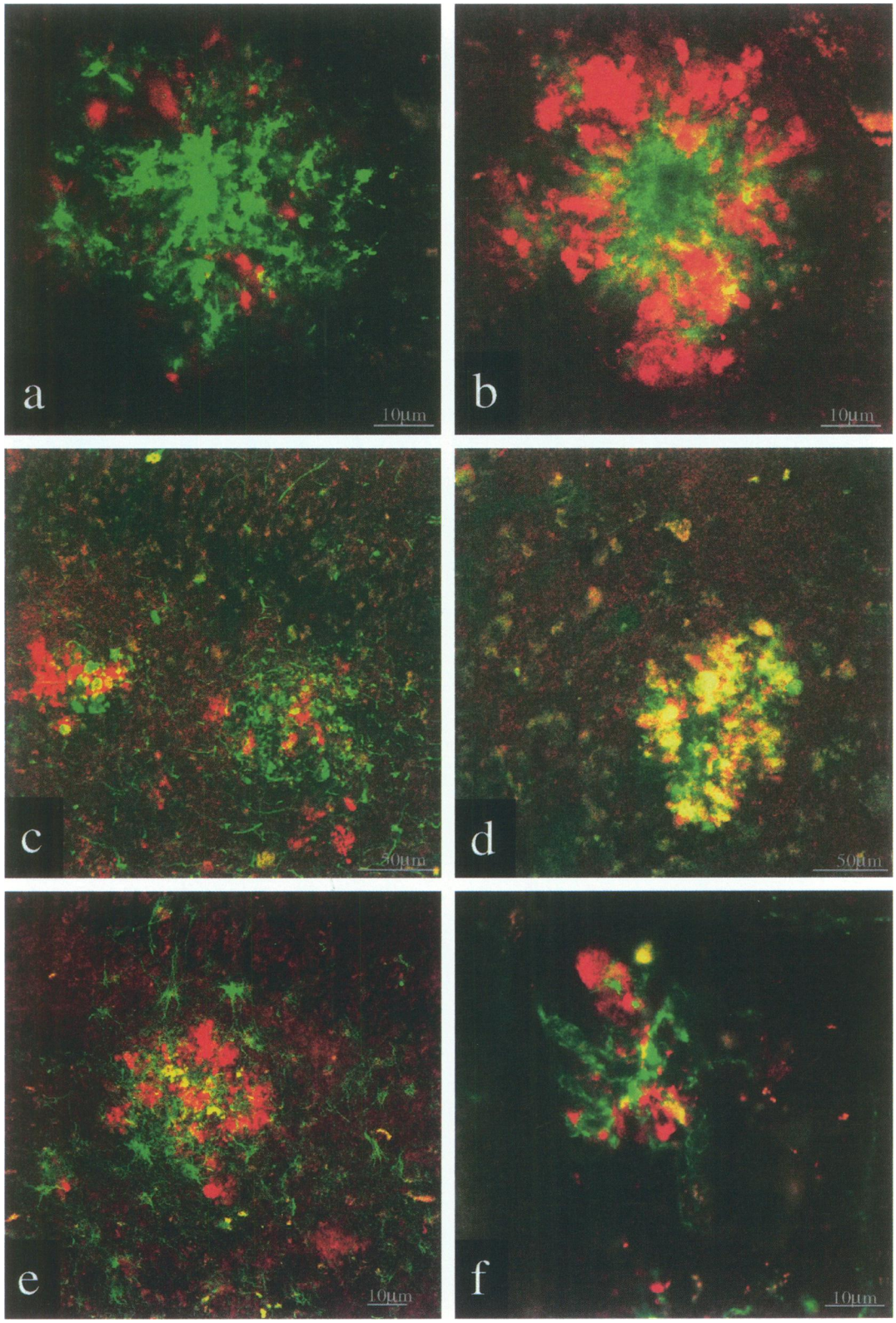

Figure 5. *Confocal images of double staining of IL-8RB-positive plaques.* **a** *and* **b**: *IL-8RB (6C6, red)* versus *Aβ (10D5, green) staining.* **a** *and* **b** *are sections at different levels of the plaque.* **c**: *IL-8RB* versus *NFT (PHF-1 antibody, green) staining.* **d**: *IL-8RB* versus *βPP (7H5, anti-KPI, green) staining.* **e**: *IL-8RB* versus *glial fibrillary acidic protein (for astrocytes, green) staining.* **f**: *IL-8RB* versus *MHC class II (LN-3 for microglial, green) staining. Yellow indicates co-localization of red and green images.* **a**, **b**, **e**, *and* **f** *are from the same case as in Figure 1a;* **c** *and* **d** *are from an 85-year-old male patient with AD for 15 years.*

In the CNS, data on IL-8 have been scarce. Some glioblastoma and cultured astrocytes have been shown to produce IL-8.[5–7] IL-8 has been shown to prolong the survival of embryo hippocampal neurons in longer-term culture.[8] In our study, the strong IL-8RB staining on pyramidal neurons and neuritic plaques and the co-localization of IL-8RB staining with βPP-positive neurites but not PHF-positive neurites are particularly interesting. It has been suggested that neuritic plaques are the result of aberrant neuronal sprouting.[24–27] As more than 50% of βPP-positive neurites in plaques have been reported to be immunoreactive for the growth-associated protein (GAP-43),[25] and GAP-43 has been associated with neurite growth and axonal regeneration,[28,29] the high βPP expression and the lack of PHF-1 immunoreactivity in these IL-8RB-positive neuritic plaques suggest that at least a certain proportion of these neurites are aberrantly regenerating neurites.

Based on our immunohistochemical observations of IL-8RB in normal and AD brain and the report of a neurotrophic effect of IL-8, we formulated the following hypothesis. The constitutive presence of IL-8RB in normal neurons and the expression of IL-8 by glial cells suggests that IL-8 may mediate some neuronal-glial interactions. In AD, we postulate that Aβ, free radicals, or other toxic stimuli stimulate astrocytes or microglia to secrete cytokines, such as IL-8 or other potential IL-8RB ligands. Those cytokines can act on IL-8RB-positive neurons and neurites to respond to these insults. The co-localization of IL-8RB with βPP-positive (and not with PHF-1-positive) neuronal processes supports the idea that these neurites are regenerative.

By contrast with IL-8RB, we were unable to detect IL-8RA or IL-8. Given the small amounts and relatively short half-lives of cytokines, they are difficult to detect by immunohistochemistry, so that this result may well reflect technical issues. We are further evaluating the presence and anatomical distribution of IL-8RA, IL-8, and other chemokines and their receptors in brain using more sensitive methods.

In addition to our current observations on IL-8RB, a recent paper reports that the Duffy antigen, a promiscuous chemokine receptor, is expressed in cell bodies and processes of Purkinje cells in the cerebellum.[30] The different cellular distributions of IL-8RB and Duffy antigen suggests different roles for these two chemokine receptors found in the CNS. It seems likely that other chemokine and cytokine receptors will also be found in the CNS. For example, IL-2 receptor was also reported to be present in the CNS by Rogers and colleagues.[31] The widespread presence of chemokine receptors in brain indicates that chemokines and their receptors may play a previously unanticipated role in the CNS. More studies are underway to explore their potential role in the CNS and in the progression of AD.

Acknowledgments

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