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1–40 β-Amyloid Protein Fragment Modulates the Expression of CD44 and CD71 on the Astrocytoma Cell Line in the Presence of IL1β and TNFα

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The modulation of CD44, VCAM-1 and CD71 expression was analysed by flow cytometry in the 1321N1 astrocytoma cell line in the presence of interleukin-1β (IL1β), tumour necrosis factor-α (TNFα) and 1–40 or 25–35 β-amyloid (Aβ) fragments. The percentage of 1321N1 astrocytoma cell line expressing these markers increased significantly after treatment with TNFα or IL1β. The presence of Aβ 1–40 fragment, alone or in combination with IL1β, induced an increase in the percentage of cells expressing CD44, but not VCAM-1. However, the concomitant presence of Aβ 1–40 fragment and of IL1β or TNFα caused an increase in the percentage of CD71 positive cells. In contrast, the shorter Aβ 25–35 fragment was always inactive. These results indicates that Aβ 1–40 fragment, in association with cytokines, can activate this astrocyte-derived cell line and add further elements in favour of the hypothesis that β-amyloid can act as immunological mediator.
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The accumulation of beta-amyloid, a 39–43 amino acid long protein, in the brain in Alzheimer's disease (AD) is the basis of the formation of neuritic plaques that cause neuronal damage and dysfunction through the activation of microglia and astrocyte cells (Selkoe, 1994; Pike et al., 1995; Malchiodi-Albedi et al., 2001). At plaque site a variety of beta-amyloid fragments (Aβ 1–40 or Aβ 25–35) are also present. They derive from the processing of amyloid precursor protein (APP) carried out by astrocytes or microglia cells and appear to be associated with different proteoglycans (McLaurin et al., 1999) or collagens (van Horssen et al., 2002). Beta-amyloid fragments participate to the activation of microglia and astrocytes by inducing the production of inflammatory cytokines like interleukin 1β (IL1β), tumour necrosis factor-α (TNFα), as well as toxic mediators like nitric oxide (Selkoe, 1994; Sheng et al., 1996). It is not clear, however, whether beta-amyloid and its fragments modulate the expression of adhesion molecules or activation markers in human astrocytes, as well, thus participating to the amplification of the inflammatory response. Data in the literature indicate that CD44, a ligand for hyaluronic acid and other proteoglycans, is upregulated on the surface of astrocytes present near the vessel of senile plaques in AD patients (Akiyama et al., 1993; Kaaijk et al., 1996; Snow et al., 1996). Vascular cell adhesion molecule-1 (VCAM-1) is also overexpressed on neurons in AD upon amyloid stimulation (Du Yan et al., 1997) and induced by IL1β and TNFα on astrocytoma (Moynagh et al., 1994; Oh et al., 1998; Winkler and Benveniste, 1998; Bourke and Moynagh, 1999). Also CD71, the transferrin receptor, has been described on the surface of rat astrocytes (Qian

Abbrevations: VCAM-1, vascular cell adhesion molecule-1; APP, amyloid precursor protein; Aβ 1–40, β-amyloid 1–40 protein fragment; Aβ 25–35, β-amyloid 25–35 protein fragment; AD, Alzheimer's disease; FBS, foetal bovine serum; PBS, phosphate-buffered salt solution; TNFα, tumour necrosis factor α; IL-1β, Interleukin 1 β.

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et al., 1999) and in the central nervous system (CNS) of AD patients (Morris et al., 1994; Connor and Menzies, 1995). It has been postulated that metals may use the transferrin-ferritin system to gain access to the cells in neurodegenerative diseases (Frederickson, 1989; Connor and Menzies, 1995; Moos and Morgan, 2000).

In this study, we utilised a human astrocytoma cell line (1321N1) to investigate the expression of CD44, VCAM-1 and CD71 in the presence of Aβ 1–40 or Aβ 25–35 fragment. As control, classical astrocyte activators, IL1β and TNFα, were used. The human astrocytoma 1321N1 cell line has been chosen since it represents a useful and reliable model to study the properties of astrocyte and their response to immunological stimulation (Trejo et al., 1994; Li et al., 1998; Bourke and Moynagh, 1999).

MATERIALS AND METHODS

Culture medium and reagents

Dulbecco's modified Eagle's medium (DMEM) (Whittaker Bioproducts, Walkersville, MD) supplemented with 100 U/ml of penicillin, 2 mM glutamine, 100 mg/ml streptomycin, 20 mM Hepes buffer (17-737E, Whittaker Bioproducts) and 10% foetal bovine serum (FBS defined) (SH30070, Hyclone Laboratories, Inc., Cramlington, UK) was used as complete medium (CM) in all the experiments. All reagents were tested for endotoxin contamination by the LAL assay (17-737E Whittaker Bioproducts).

Recombinant IL1β and TNFα (Peprotech, London, UK) were diluted in DMEM, stored, frozen at −20°C in aliquots and used at doses ranging between 0.25–1 ng/ml and 20–200 ng/ml, respectively. The two amyloid β protein fragments, Aβ 25–35 and Aβ 1–40, were purchased from Sigma (A4559 and A5813, St Louis, MO), solubilised in sterile water to 1 mg/ml, diluted with CM before usage in a range from 5–40 μg/ml to 50–100 ng/ml, respectively.

Cell cultures

The human astrocytoma cell line 1321N1 employed in all the experiments was purchased from American Type Culture Collection (ATCC, Rockville, MD). It was cultured in CM in 75-cm^2 tissue culture flasks (Costar, Corning, NY) and maintained at 37°C in a 5% CO_2 humidified atmosphere. For passage, monolayers were rinsed once with phosphate-buffered salt solution (PBS), then dislodged with 0.05% (w/v) trypsin (Seromed, Biochrom KG, Berlin, Germany) in PBS solution and resuspended in CM. For all the experiments, the cells were used at passages between 15 and 30.

Cytokines and treatments

1321N1 cells were distributed in 24-well culture plates (Costar) at a concentration of 2.5×10^5 cells/well in 1 ml final volume and incubated for 24 h at 37°C in 5% CO_2 in the presence of various doses of amyloid Aβ 25–35 and Aβ 1–40 fragments. The doubling time for this astrocytoma cells line was 72 h. Therefore, the number of the cells at the end of treatment would be 5×10^5/well, approximately. For some experiments, a time-dependent kinetic curve of response to amyloid β fragments was also monitored.

Cell viability

Viability of the cells was assayed by trypan blue exclusion after stimulation with cytokines and amyloid β fragments at all the doses used.

Flow cytometric analysis

The expression of VCAM-1, CD44 and CD71 molecules on the surface of the astrocytoma cells was evaluated by flow cytometric analysis.

After 24 h, cell stimulation was blocked by removing the supernatant and washing the cell monolayers with PBS. Cells were treated with 0.05% (w/v) trypsin (Seromed, Biochrom KG) in PBS solution, washed once in PBS supplemented with 10% FBS and dispensed in polystyrene round-bottom tubes (Falcon 2052, Becton Dickinson Labware, Franklin Lakes, NJ) and centrifuged for 10 min at 1600 rpm. The pellet was resuspended in 100 μl of PBS and incubated at 4°C for 40 min in the dark using 10 μl of mouse IgG1 Fluorescein isothiocyanate (FITC) conjugated anti-CD44 antibody (IM1219, J.173 clone, Coulter Immunotech, Marseille, France) or mouse $IgG2_A$ anti-VCAM-1 (BBA22, R&D Systems, Inc., Minneapolis, MN) or phycoerythrin (PE/RD1) conjugated mouse IgG1 antibody anti-CD71 (IM 2001, YDJ1.2.2 clone, Coulter Immunotech). After the incubation with monoclonal antibodies (mAbs), the cells were washed with PBS and the pellet resuspended in 4% paraformaldehyde in PBS.

Astrocytoma cells were incubated with fluorocrome-labelled mAbs and analysed using forward scatter and side scatter properties. Analyses were performed using a Coulter Epics XL flow cytometer (Coulter Electronics, Inc., Miami Lakes, FL) equipped with an air-cooled 15-mW argon ion laser operating at 488 nm. Multiparametric data were collected for 10,000 events and analysed. Data were collected using linear amplifiers for forward scatter and side scatter and logarithmic amplifiers for FL1 and FL2. Samples were first run using a single fluorocrome-stained preparation for colour compensation or single mAbs isotype-matched IgG1PE-conjugated (IM0639 or IM0670, 679.1 Mc7 clone, Coulter Immunotech) or FITC-conjugated $IgG2_A$ (IC003F, 20102.1 clone, R&D Systems), respectively.

Statistical analysis

All the tests were performed at least three times, in triplicate. Data are expressed as mean ± SD. The statistical analysis was performed by Student's *t*-test for paired data. Differences with $P < 0.05$ were considered significant.

RESULTS

When the 1321N1 cell line was treated with TNFα or IL1β, a significant and dose-dependent increase in the percentage of cells expressing CD44, VCAM-1 or CD71 was observed. Out of six different experiments, maximal induction of CD44 expression was seen with 50 ng/ml of TNFα (35.2% ± 4.0) and 1 ng/ml of IL1β (41.4% ± 5.6) (Fig. 1, part a). The percentage of CD44 positive cells did not change significantly with higher doses of both IL1β and TNFα.

Significant increase, above untreated control, of VCAM-1-expressing cells was obtained with 100 ng/ml

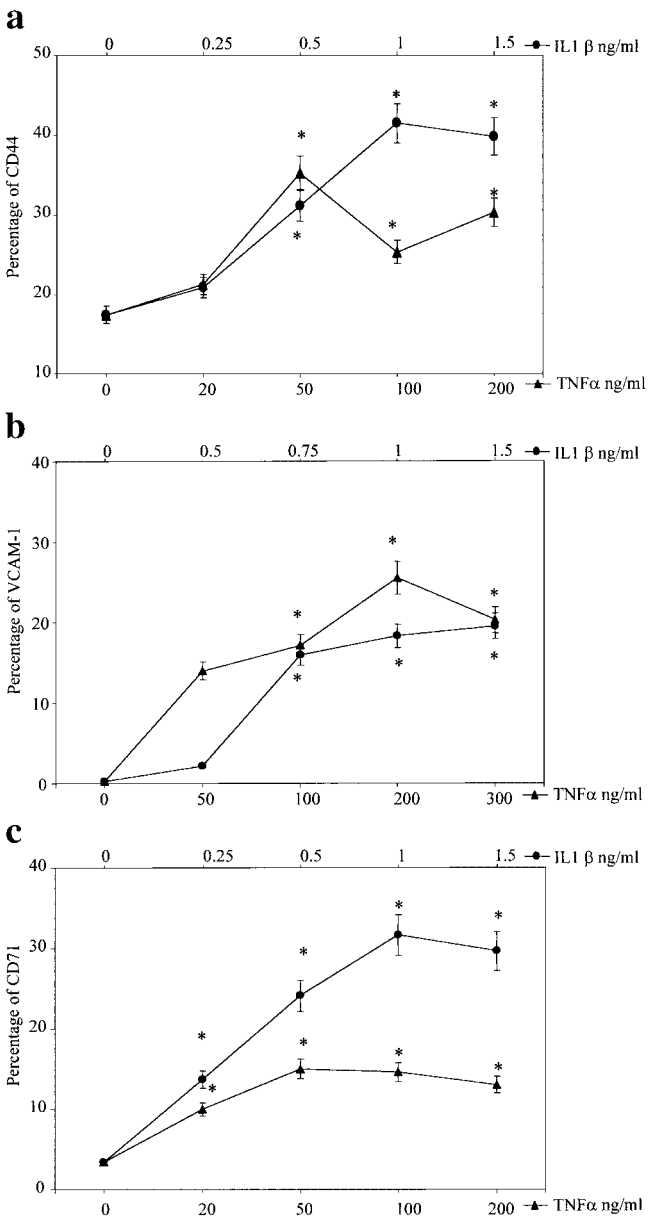

Fig. 1. Expression of CD44 (**a**), VCAM-1 (**b**) and CD71 (**c**) on astrocytoma cell line 1321N1, 24 h after stimulation with different doses of TNFα (▲) or IL1β (●). Each point is expressed as a percentage and represents the mean ± SD of six different experiments performed in the same conditions. $^*P < 0.05$ between cytokine stimulated compared to unstimulated 1321N1 cells.

of TNFα (25.5% ± 4.5) or 1 ng/ml of IL1β (18.2% ± 1.2). No further increase of VCAM-1 was seen with higher doses of TNFα or of IL1β (Figure 1, part b).

IL1 and, to a lesser extent TNFα, also enhanced in a significant manner the number of CD71 positive 1321N1 cells. On average, out of six different experiments, the maximum percentage of CD71-positive cells was 31.67% ± 4.2 and 15.0% ± 2.2 with 1 ng/ml of IL1β or 50 ng/ml of TNFα, respectively. Again higher doses of these cytokines did not induce a further increase in the expression of CD71 on 1321N1 cells. (Figure 1, part c).

When the 1321N1 cell line was stimulated with Aβ 1–40 or Aβ 25–35 amyloid fragments, only the Aβ 1–40 fragment was able to significantly increase the expression of CD44. With 50 ng/ml of Aβ 1–40 fragment, on average, 37.4% ± 6.3 CD44-positive cells were observed. No further increase was seen up to 200 ng/ml of Aβ 1–40. On the contrary, the Aβ 25–35 fragment alone was inactive at all the doses tested. (Figure 2, part a).

Both the Aβ 25–35 and the Aβ 1–40 fragments, when used alone, were unable to modulate the expression of VCAM-1 or CD71 on the 1321N1 cells at any the doses used (Figure 2, parts b and c).

The expression of CD44 on 1321N1 astrocytoma cells after stimulation with 50 ng/ml of Aβ 1–40 fragment was time-dependent: it increased almost two fold between 18

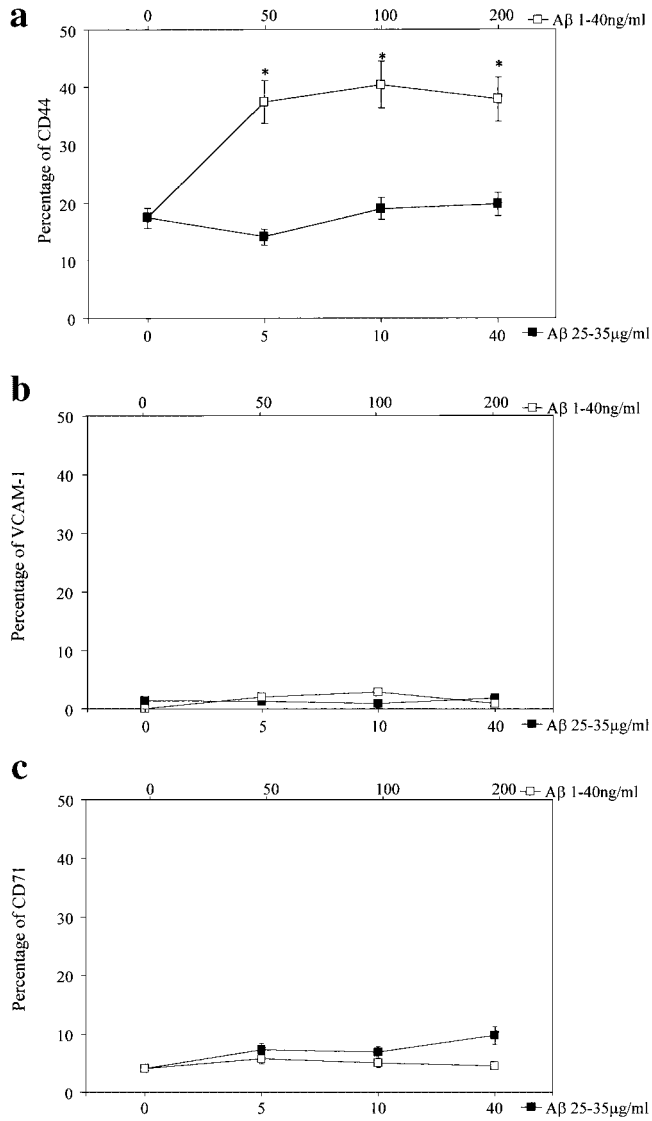

Fig. 2. Expression of CD44 (**a**), VCAM-1 (**b**) and CD71 (**c**) on astrocytoma cell line 1321N1, after 24 h of stimulation with 50–200 ng/ml of Aβ 1–40 (□) or 5–40 μg/ml of Aβ 25–35 (■) fragments. Each point is expressed as a percentage and represents the mean ± SD of six different experiments performed in the same conditions. $^*P < 0.05$ between Aβ 1–40 stimulated compared to unstimulated 1321N1 cells.

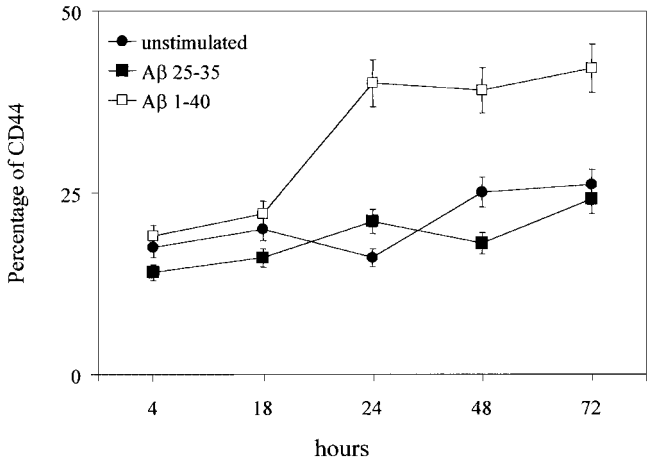

Fig. 3. Kinetics of percentage of CD44 expression on astrocytoma cell line 1321N1 after stimulation with 50 ng/ml of Aβ 1–40 (□) or 40 μg/ml of Aβ 25–35 (■) fragments. The solid black circles represent the spontaneous expression of CD44 at different time-points in the absence of β amyloid fragments. This is a representative experiment out of three performed in the same conditions.

and 24 h of treatment and remained elevated up to 72 h. However, no modulation of CD44 was seen with Aβ 25–35 fragment even when the treatment was prolonged for 72 h (Figure 3).

We then asked the question of whether the stimulation of 1321N1 cells with Aβ 25–35 (40 μg/ml) or Aβ 1–40 (50 ng/ml) fragments in the presence of suboptimal doses of IL1β (0.25 ng/ml) or TNFα (50 ng/ml) resulted in modulation of the activation markers by astrocytes. Figure 4 shows the results averaged from four different experiments. The treatment of 1321N1cells with IL1β in the presence of Aβ 1–40 fragment, resulted in a significant increase in CD44-positive cells (55.7 ± 4.5) in comparison with control cells treated with IL1β (23.3 ± 1.5) or Aβ 1–40 (30.3 ± 4.4) only. However, no significant differences were seen after co-stimulation with IL1β plus Aβ 25–35 fragment or by using TNFα, instead of IL1. (Fig. 4).

Different results were obtained when the expression of CD71 was evaluated in the same experimental conditions (Fig. 5). Again the co-stimulation with IL1β plus the Aβ 1–40 fragment induced a significant increase in percentage of CD71-positive cells (28.6 ± 6.1) compared to the cells treated with IL1β (13.2 ± 1.5) or Aβ 1–40 (6.5 ± 3.0), only. Different from CD44, CD71 was increased by TNFα in the presence of Aβ 1–40 (21.3 ± 5.5), but not of the Aβ 25–35 fragments.

In the same experimental conditions, no differences were observed in the percentage of VCAM-1-expressing cells after stimulation with suboptimal doses of IL1β or TNFα in the presence of the Aβ 1–40 or the Aβ 25–35 fragments (data not shown).

DISCUSSION

In neurodegenerative disorders, including AD, the activation of microglia or astrocytes seems to contribute to the neuronal dysfunction. In particular, the astrocytes present around the senile plaques of amyloid deposits could play an active role in initiating and/or promoting the inflammatory process by modulating the level of cytokines and the expression of adhesion molecules or activation receptors (Gitter et al., 1995; Pike et al., 1995).

To verify this hypothesis, we utilised the 1321N1 astrocytoma-derived cell line as an experimental model (Trejo et al., 1994; Li et al., 1998; Bourke and Moynagh, 1999) to study the modulation of CD44, VCAM-1 or CD71 after treatment with two different cytokines, IL1β and TNFα, and the amyloid-β (Aβ) fragments, that are largely present in amyloid plaques. The results

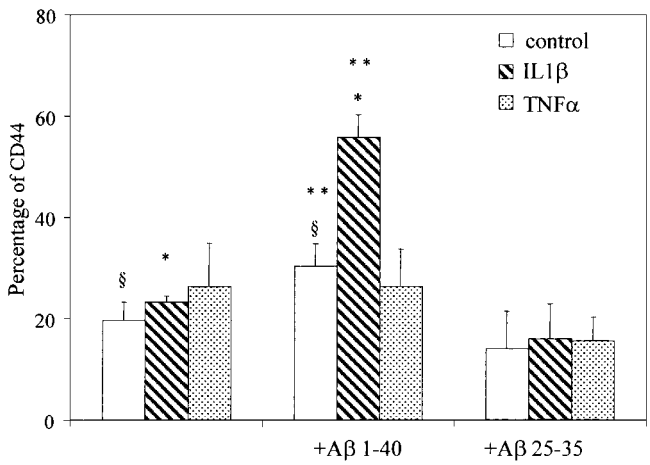

Fig. 4. Effects of Aβ 1–40 (50 ng/ml) or Aβ 25–35 (40 μg/ml) fragments on the expression of CD44 on the astrocytoma 1321N1 cell line only (**blank columns**), in the presence of IL1β 250 pg/ml (**striped columns**) or TNFα 50 ng/ml (**dotted grey columns**). Data are represented as mean ± SD of four separate experiments performed in the same conditions. $^{*}P < 0.01$ between Aβ 1–40 plus IL1β treated compared to IL1β stimulated 1321N1 cells. $^{**}P < 0.01$ between Aβ 1–40 plus IL1β treated compared to Aβ 1–40 stimulated 1321N1 cells. §$P < 0.05$ between Aβ 1–40 plus IL1β treated compared to unstimulated 1321N1 cells.

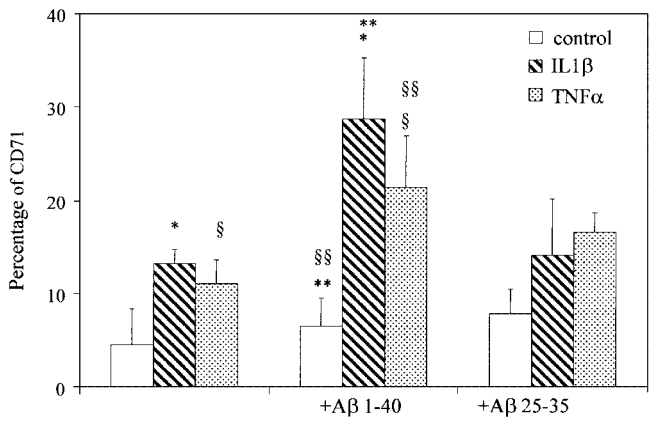

Fig. 5. Effects of Aβ 1–40 (50 ng/ml) or Aβ 25–35 (40 μg/ml) fragments on the expression of CD71 on the astrocytoma 1321N1 cell line only (**blank columns**), in the presence of IL1β 250 pg/ml (**striped columns**) or TNFα 50 ng/ml (**dotted grey columns**). Data are represented as mean ± SD of four separate experiments performed in the same conditions. $^{*}P < 0.01$ between Aβ 1–40 plus IL1β treated compared to IL1β stimulated 1321N1 cells. $^{**}P < 0.01$ between Aβ 1–40 plus IL1β treated compared to Aβ 1–40 stimulated 1321N1 cells. §$P < 0.05$ between Aβ 1–40 plus TNFα treated compared to TNFα stimulated 1321N1 cells. §§$P < 0.05$ between Aβ 1–40 plus TNFα treated compared to Aβ 1–40 stimulated 1321N1 cells.

indicated that IL1β and TNFα induce an increase in the percentage of astrocytes positive for CD44, VCAM-1 or CD71. Overall, IL1β appears to be a stronger signal for human astrocytes compared to TNFα.

Unstimulated 1321N1 astrocytes express low levels of CD44 that is significantly upregulated by IL1β and, to a lesser extent by TNFα treatment. After stimulation with IL1β, more than 40% of astrocytes express CD44, while only 30% positive cells are counted after treatment with TNFα. VCAM-1 and CD71, undetectable in untreated cells, were both increased by IL1β or TNFα. This is the first report showing an enhanced CD71 expression on human astrocytoma cells in vitro. So far only rat astrocytes were shown to express CD71 (Qian et al., 1999). These data parallel the observation of an increased expression of transferrin receptors in senile plaques or near the microvessels in AD patients (Kalaria et al., 1992; Connor and Menzies, 1995) indicating that this receptor may be of relevance in plaque arrangement. In fact, changes in the ability of the cells to express binding receptors for iron may identify an activated cell population exposed to iron-induced oxidative stress.

These data also extend previous observations that IL1β induces an increase of VCAM-1 expression on 1321N1 astrocytoma, but it is the first time that similar results are obtained with TNFα in this cell population. (Moynagh et al., 1994; Bourke and Moynagh, 1999). It thus appears that the cytokine microenvironment participates to the activation of astrocytes and could be responsible for the increased expression of activation markers reported in the brain of Alzheimer's patients (Akiyama et al., 1993; Morris et al., 1994; Connor and Menzies, 1995; Du Yan et al., 1997).

Together with cytokines, a large amount of amyloid protein and its fragments are present at plaque site. The treatment of astrocytoma cells with the amyloid Aβ 1–40 fragment, but not with the Aβ 25–35 fragment, upregulated the expression of CD44. This is consistent with previous observations that the Aβ 25–35 fragment is unable to induce cytokine production in primary rat astrocyte (Forloni et al., 1997) or nitric oxide in peritoneal mouse macrophages when used alone (Klegeris et al., 1994). This effect could be either due to the presence of active amino-acid sequences in the Aβ 1–40 fragment that are lost in the Aβ 25–35 fragment; or to the length and conformation of the fragment critical for cell activation (Meda et al., 1996). Neither protein fragments influenced the expression of VCAM-1 and CD71 on astrocytes.

The fact that Aβ 1–40 induced a long lasting expression of CD44 on astrocytoma cells may have an important pathogenetic role, since CD44 through the binding to hyaluronic acid, proteoglycans and collagens may favour the accumulation of these products at plaque site (Snow et al., 1996; McLaurin et al., 1999; van Horssen et al., 2002). CD44-positive astrocytes will directly participate to the arrangement of the plaques. Further support to this hypothesis is provided by the data that suboptimal doses IL1β in the presence of Aβ 1–40 fragment induce a strong and significant increase of CD44 on astrocytoma cell. IL1β is known to possess an important role in plaque evolution (Griffin et al., 1995); it is produced by microglial cells or by astrocytes located in proximity of the deposits of amyloid β fragments (Selkoe, 1994; Sheng et al., 1996). The upregulation of CD44 expression may well represent one of the earliest evidences of astrocyte activation.

TNFα does not seem to substitute for IL1β as costimulus with Aβ 1–40 fragment in the induction of CD44 confirming that, at least in this experimental model, TNFα is less relevant than IL1β.

Similarly to CD44, also the expression of CD71 was increased by the Aβ 1–40 fragment, but only when minimal doses IL1β or TNFα were used as costimulus. Again the shorter Aβ 25–35 fragment was inactive. These data suggest that the activation of the transferrin receptor in the brain in proximity of senile plaques could be due to the combined action of amyloid fragment and immunologically active molecules released by microglia or astroglia during the pathogenic process. (Giulian et al., 1988; Goldgaber et al., 1989; Buxbaum et al., 1992; Gitter et al., 1995; Griffin et al., 1995; Buxbaum et al., 1998; Sheng et al., 1996).

From our data it is emerging that VCAM-1 expression on astrocytes is upregulated only by treatment with inflammatory cytokines and not by the Aβ fragments, either alone or in combination with suboptimal doses of IL1β or TNFα. This is similar to what is reported in other brain pathologies where an inflammatory response is present, such as in AIDS dementia complex or in the Multiple Sclerosis. (Seilhean et al., 1997; Lee and Benveniste, 1999).

In conclusion, the results of this study indicate that inflammatory cytokines, IL1β and TNFα, may play a crucial role in the development of active lesions by increasing the expression of CD44, VCAM-1 or CD71 on astrocytoma cells. The amount and the length of the amyloid protein present at plaque site is also an important variable, since only the Aβ 1–40 fragment, but not the shorter Aβ 25–35 peptide, is able to increase in a dose dependent manner the percentage of CD44-positive astrocytes and to synergise with the cytokines to modulate the expression of CD44 and CD71 on astrocytes.

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