



*Review*

## Mechanisms of Immune Regulation in Alzheimer's Disease: a Viewpoint

FLORENTINE MARX, IMRICH BLASKO and BEATRIX GRUBECK-LOEBENSTEIN\*

Institute for Biomedical Aging Research, Austrian Academy of Sciences, Rennweg 10, A-6020 Innsbruck, Austria

**Abstract.** The immune system may play an important role in the neurodegenerative process in Alzheimer's disease (AD). Complement components, eicosanoids and cytokines are found in cerebral amyloid plaques. These inflammatory proteins may stimulate the amyloid  $\beta$  ( $A\beta$ ) production, support its aggregation and increase its cytotoxicity, thus aggravating the pathology of AD.  $A\beta$  may trigger their release from activated microglia and astrocytes which are the main sources of these proteins. However, there are also indications for a protective role of the immune system against the development of AD. Microglial cells have been shown to degrade  $A\beta$  and recent evidence suggests a role of autoreactive  $A\beta$ -specific T cells in the elimination of the peptide. This mechanism seems to be impaired in the majority of patients with AD. An  $A\beta$ -specific immune reaction may thus represent a natural defence mechanism directed against the accumulation of dangerous amyloidogenic substances. Impairment of the immune system and the failure to eliminate a toxic metabolite can be the basis for a chronic non-specific inflammatory process in the brain, as described above. AD is a good example how an immune response may lead to tissue destruction and neuronal loss instead of maintaining the integrity of the body.

**Key words:** Alzheimer's disease; Alzheimer amyloid precursor protein; amyloid  $\beta$ ; cytokines; T lymphocytes; autoreactivity; inflammation.

---

Amyloid  $\beta$  ( $A\beta$ ) is one of the main plaque components in the brain of Alzheimer's disease (AD) patients. This 39–43 residue peptide is cleaved by still unknown proteolytic enzymes from the larger Alzheimer amyloid precursor protein (APP)<sup>19</sup>, a protein of 695–770 amino acids. These isoforms are generated by alternative splicing of a single gene located on chromosome 21. APP is a transmembrane glycoprotein and is expressed in most neuronal and extraneuronal tissues<sup>37</sup>. It can either be processed to release a large secretory product or be metabolized in an endosomal/lysosomal pathway without secretion<sup>36</sup>. While the former pathway cuts APP within the  $A\beta$  sequence and thus precludes amyloid formation, the latter pathway is considered as amy-

loidogenic<sup>14</sup>.  $A\beta$  is, however, found in cerebral spinal fluid and blood plasma of normal individuals<sup>38</sup>. While the physiological role of APP has not been fully elucidated, it is getting increasingly clear that the  $A\beta$  protein may play a central role in the pathogenesis of AD<sup>37</sup>. The harmful effect of  $A\beta$  obviously depends on its quantity and aggregation. Thus, it has been shown that overproduction of  $A\beta$  (1–40) or of the more easily aggregating form  $A\beta$  (1–42) is a typical feature of states with an AD pathology, such as for instance Down's syndrome<sup>45</sup> or early onset AD due to familial mutations in the APP gene<sup>8</sup>. Alternatively, decreased clearance of soluble  $A\beta$  could also result in locally increased concentrations. While soluble  $A\beta$  is relatively harmless,

---

\* To whom all correspondence should be addressed.

aggregated amyloid has been shown to be cytotoxic<sup>17</sup> and is at present believed to lead to neurodegenerative changes in the brain<sup>5, 37</sup>. Amyloid aggregation leads to plaque formation which is still enhanced by amyloid-associated proteins such as  $\alpha 1$  antichymotrypsin<sup>1</sup>, complement components<sup>32</sup>, serum amyloid<sup>6</sup> or heparan sulfate proteoglycans<sup>42</sup>. Recently, the immune system is believed to play a decisive role in determining local concentrations as well as the toxicity of amyloid. In the brain microglial cells orchestrate the endogenous immune response. They carry most markers of innate immunity and can also express MHC II molecules. They interact with astrocytes, which sustain the functional integrity of neurons and contribute extracellular matrix proteins. Immune cells and mediators may affect the production of A $\beta$ , may hamper or support its aggregation, can control its cytotoxicity versus neuronal or other cells, and may influence its sequestration. These different immunological functions will be discussed in the following.

### **The Effects of Non-Specific Innate Immunity on the Development of AD**

#### *Influence on the production and metabolism of APP*

Inflammatory cytokines have been shown to affect the production and metabolism of APP. Thus, interleukin 1 (IL-1) stimulates the synthesis of APP and its amyloidogenic metabolites<sup>34, 47</sup>. TGF- $\beta$  induces the accumulation of cellular APP<sup>27</sup> and may initiate or promote amyloidogenesis<sup>51</sup>. Interferon  $\gamma$  (IFN- $\gamma$ ) inhibits the production of secreted APP (APPs)<sup>34</sup>. While tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) alone does not have any effect on APP production and its metabolism, in combination with IFN- $\gamma$  it induces a rapid increase in the transcription and production of APP. This change is followed by an inhibition of APPs secretion and a pronounced release of A $\beta$  into the culture medium<sup>3</sup>. Thus inflammatory components can exacerbate the fundamental pathology in AD.

#### *Influence on amyloid aggregation and plaque formation*

It has been demonstrated that A $\beta$  deposits in the brain of patients with AD are closely associated with various complement components such as C1q, C3d, C4d and C5<sup>23</sup>. These complement factors may activate C5b-C9, which will consequently promote neuronal death when assembled on the plasma membrane<sup>15</sup>. In addition to this potentially neurotoxic effect, C1q can

bind to A $\beta$ <sup>18</sup>, induce its aggregation and increase its cytotoxicity. C1q binding to A $\beta$  may also be a trigger mechanism for the above mentioned activation of the classical complement cascade<sup>31</sup>. High numbers of microglial cells are found around the mature plaques of AD brains<sup>20</sup>. They express increased levels of Fc receptors, MHC class I and class II molecules, as well as  $\beta 2$  integrins and the vitronectin receptor<sup>7, 24</sup>. They may also produce cytokines such as IL-1, IL-6 and TNF- $\alpha$ <sup>26, 49</sup>. A quantitative link between A $\beta$  plaque formation and microglial activation has been described in an animal model<sup>9</sup>. Inflammatory mediators produced by activated microglial cells can aggravate plaque formation. This can lead to a vicious circle, as cytokine and nitric oxide (NO) production can be augmented by aggregated A $\beta$ , particularly in the presence of other stimulatory agents such as IL-1 $\beta$  or IFN- $\gamma$ <sup>11, 26</sup>.

#### *Influence on the toxicity of A $\beta$*

Cytokines may also be involved in the development of neuropathology. Although TNF- $\alpha$  has been attributed neuroprotective qualities by some authors<sup>2</sup>, it is mainly regarded as a potentially destructive agent<sup>48</sup>. Thus, it has been described as mediating the production of toxic free radicals in glial cells and as contributing to the process of neuronal degeneration<sup>26</sup>. Although TNF- $\alpha$  may be harmless in the absence of aggregated A $\beta$ , it can support the neurodegenerative process once amyloid aggregation has started<sup>4</sup>.

### **The Protective Role of the Antigen-Specific Acquired Immunity in AD**

#### *Effects on the elimination of A $\beta$*

Several lines of evidence have led to the hypothesis that the immune system may attempt to remove toxic amyloidogenic APP metabolites. This could represent a physiological protective mechanism. Sequestration may be influenced by the presence of microglia or macrophages<sup>20, 29, 39</sup>, or by protein-protein interactions such as with apolipoprotein E<sup>43</sup>, transthyretin<sup>35</sup>, or autoantibodies<sup>10, 28</sup>. Brain-specific antibodies have indeed been described<sup>30</sup> and two reports on the occurrence of A $\beta$ -specific autoantibodies have been published<sup>10, 28</sup>. Although this has led to the suggestion that autoimmune mechanisms might contribute to the pathology of AD<sup>41</sup>, it may on the other hand be regarded as a sign of ongoing protective autoreactivity initiated by the organism to defend against disease and to repair damage. This type of mechanism has been described in periph-

eral organs and situations such as uncontrolled growth or tissue damage<sup>12, 13, 44</sup>. The first step to trigger amyloid-specific adaptive immune reactivity would be the endocytosis of A $\beta$  by antigen-presenting cells, its processing and its consecutive presentation via MHC molecules. Dendritic cells, the most potent antigen-presenting cell type, can indeed endocytose amyloid even in its aggregated form<sup>33</sup>. TRIEB et al.<sup>46</sup> detected A $\beta$ -reactive immune cells in healthy individuals and demonstrated that soluble A $\beta$  can induce IL-2 receptor expression and proliferation in peripheral T lymphocytes. Further characterization of A $\beta$ -specific T cells revealed a predominantly CD8<sup>+</sup> phenotype and a TH1/TC1 cytokine production pattern with high IFN- $\gamma$  secretion, but nearly no IL-4 production. Additionally, A $\beta$ -specific T cells are able to recognize and subsequently lyse A $\beta$  overproducing cells *in vitro*<sup>21</sup>. How these cells might participate in the elimination of amyloidogenic substances *in vivo* remains a subject of speculation. CD8<sup>+</sup> T cells could be activated by soluble A $\beta$  produced in the periphery, pass through the blood/brain barrier due to their activated stage and patrol through the brain<sup>50</sup>, where they could eliminate single A $\beta$ -overproducing cells. CD4<sup>+</sup> amyloid-specific T cells could, on the other hand, help B cells to produce A $\beta$ -specific autoantibodies. These could bind A $\beta$  and support its degradation, hereby decreasing the whole body load of amyloidogenic substances. Immune activation by A $\beta$  seems to be impaired in patients with AD, as their peripheral T cells fail to proliferate, in spite of intact CD25 expression following stimulation with A $\beta$ <sup>46</sup>. It is thus intriguing to suggest that AD patients have been exposed to higher concentrations or to different antigenic epitopes of A $\beta$ , due to an altered APP metabolism. This could result in T cell anergy instead of full activation. Patients with AD, in whom certain immune functions may be disturbed<sup>40</sup>, may be particularly prone to develop this type of defect. Inability to raise an antigen-specific acquired immune response may lead to the failure of the organism to avoid amyloid aggregation and its toxic consequences and could indirectly support the maintenance of a chronic overreaction of the innate immune system. Due to its immunologically privileged position, the brain may thus be particularly vulnerable.

## Conclusion

Acquired antigen-specific immunity against A $\beta$  may play a protective role against the development of AD. Patients with AD may suffer from their decreased ability to recognize A $\beta$  as an autoantigen and to elimi-

nate it as a consequence. This may lead to an imbalanced, innate, non-specific immune response in the AD brain. The notion that non-specific inflammatory factors might be involved in the maturation of amyloid plaques and the propagation of the pathology in the surrounding tissue was supported by the finding that AD was less frequent in patients with rheumatoid arthritis and other disorders chronically treated with anti-inflammatory drugs than in untreated control groups<sup>22, 25</sup>. In addition to this non-specific anti-inflammatory treatment, specific immune stimulation against A $\beta$  might help to protect from the development of amyloidosis and could represent a novel therapeutic approach to prevent AD. The possibility of inducing protective autoreactivity for an efficient elimination of damaged cells or toxic degradation products might not only be of interest for the prevention of AD, but also for other types of amyloidosis. However, as other immune responses, amyloid-specific immune reactions may also have negative consequences. Similar to the situation in chronic infectious disease, cytokine overproduction or target cell damage may occur. It should, therefore, be the goal of potential immunological interventions against amyloidosis to achieve maximal clearance of the pathogen while keeping negative side-effects as low as possible. As amyloid in its aggregated form triggers the release of potentially harmful cytokines and is cytotoxic, a specific immune response against the soluble peptide could be expected to be most effective. An exclusive propagation of CD4<sup>+</sup> T cells by appropriate vaccines and a deviation of TH1 into TH2 responses could also be tried. Intensive research work will, however, still be needed to reach this goal.

## References

1. ABRAHAM C. R., SELKOE D. J. and POTTER H. (1988): Immunohistochemical identification of the serine protease inhibitor,  $\alpha_1$ -antichymotrypsin in the brain amyloid deposits of Alzheimer's disease. *Cell*, **52**, 487–501.
2. BARGER S. W., HÖRSTER D., FURUKAWA K., GOODMAN Y., KRIEGLSTEIN J. and MATTSON M. P. (1995): Tumor necrosis factors  $\alpha$  and  $\beta$  protect neurons against amyloid  $\beta$ -peptide toxicity. Evidence for involvement of a  $\kappa$ B-binding factor and attenuation of peroxide and Ca<sup>2+</sup> accumulation. *Proc. Natl. Acad. Sci. USA*, **92**, 9328–9332.
3. BLASKO I., MARX F., STEINER E., HARTMANN T. and GRUBECK-LOEBENSTEIN B. (1999): TNF- $\alpha$  plus IFN- $\gamma$  induce the production of Alzheimer  $\beta$ -amyloid peptides and decrease the secretion of APPs. *FASEB J.*, **13**, 63–68.
4. BLASKO I., SCHMITT T. L., STEINER E., TRIEB K. and GRUBECK-LOEBENSTEIN B. (1997): Tumor necrosis factor- $\alpha$  augments amyloid  $\beta$  protein (25–35) induced apoptosis in human cells. *Neurosci. Lett.*, **238**, 17–20.

5. CHEN S. Y., WRIGHT J. W. and BARNES C. D. (1996): The neurochemical and behavioral effects of  $\beta$ -amyloid peptide (25–35). *Brain Res.*, **720**, 54–60.
6. CORIA F., CASTANO E., PRELLI F., LARRONDO-LILLO M., VAN DUINEN S., SHELANSKI M. L. and FRANGIONE B. (1988): Isolation and characterization of amyloid P component from Alzheimer's disease and other types of cerebral amyloidosis. *Lab. Invest.*, **58**, 454–458.
7. EIKELENBOOM P., ZHAN S. S., KAMPHORST W., VAN DER VALK P. and ROZEMULLER J. M. (1994): Cellular and substrate adhesion molecules (integrins) and their ligands in cerebral amyloid plaques in Alzheimer's disease. *Virchows Arch.*, **424**, 421–427.
8. ESSALMANI R., MACQ A.-F., MERCKEN L. and OCTAVE J.-N. (1996): Missense mutations associated with familial Alzheimer's disease in Sweden lead to the production of the amyloid peptide without internalization of its precursor. *Biochem. Biophys. Res. Commun.*, **218**, 89–90.
9. FRAUTSCHY S. A., YANG F., IRRIZARRY M., HYMAN B., SAIDO T. C., HSIAO K. and COLE G. M. (1998): Microglial response to amyloid plaques in APPsw transgenic mice. *Am. J. Pathol.*, **152**, 307–317.
10. GASKIN F., FINLEY J., FANG Q., XU S. and FU S. M. (1993): Human antibodies reactive with  $\beta$ -amyloid protein in Alzheimer's disease. *J. Exp. Med.*, **177**, 1181–1186.
11. GITTER B. D., COX L. M., RYDEL R. E. and MAY P. C. (1995): Amyloid  $\beta$  peptide potentiates cytokine secretion by interleukin- $1\beta$ -activated human astrocytoma cells. *Proc. Natl. Acad. Sci. USA*, **92**, 10738–10741.
12. GRUBECK-LOEBENSTEIN B., DERFLER K., KASSAL H., KNAPP W., KRISH K., LISZKA K., SMYTH P. P. A. and WALDHÄUSL W. (1985): Immunological features of nonimmunogenic hyperthyroidism. *J. Clin. Endocrinol. Metab.*, **60**, 150–155.
13. GRUBECK-LOEBENSTEIN B., LONDEI M., GREENALL C., PIRICH K., WALDHÄUSL W. and FELDMANN M. (1988): Pathogenetic relevance of HLA class II expressing thyroid follicular cells in nontoxic goiter and in Graves' disease. *J. Clin. Invest.*, **81**, 1608–1614.
14. HAASS C., KOO E. H., MELLON A., HUNG A. Y. and SELKOE D. J. (1992): Targeting of cell-surface beta-amyloid precursor protein to lysosomes: Alternative processing into amyloid-bearing fragments. *Nature*, **357**, 500–503.
15. ITAGAKI S., AKIYAMA H., SAITO H. and MCGEER P. L. (1994): Ultrastructural localization of complement membrane attack complex (MAC)-like immunoreactivity in brains of patients with Alzheimer's disease. *Brain Res.*, **645**, 78–84.
16. ITAGAKI S., MCGEER P. L., AKIYAMA H., ZHU S. and SELKOE D. J. (1989): Relationship of microglia and astrocytes to amyloid deposits in Alzheimer's disease. *J. Neuroimmunol.*, **24**, 173–182.
17. IVERSEN L. L., MORTISHIRE-SMITH R. J., POLLACK S. J. and SHEARMAN M. S. (1995): The toxicity *in vitro* of  $\beta$ -amyloid protein. *Biochem. J.*, **311**, 1–16.
18. JIANG H., BURDICK D., GLABE C. G., COTMAN C. W. and TENNER A. J. (1994): Beta-amyloid activates complement by binding to a specific region of the collagen-like domain of the C1q A chain. *J. Immunol.*, **152**, 5050–5059.
19. KANG J., LEMAIRE H.-G., UNTERBECK A., SALBAUM J. M., MASTERS C. L., GRZESCHIK K.-H., MÜLTHAUP G., BEYREUTHER K. and MÜLLER-HILL B. (1987): The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. *Nature*, **325**, 733–736.
20. MAAT-SCHIEMAN M. L., ROZEMULLER A. J., VAN DUINEN S. G., HAAN J., EIKELENBOOM P. and ROOS R. A. (1994): Microglia in diffuse plaques in hereditary cerebral hemorrhage with amyloidosis (Dutch). An immunohistochemical study. *J. Neuropathol. Exp. Neurol.*, **53**, 483–491.
21. MARX F., BLASKO I., PAVELKA M. and GRUBECK-LOEBENSTEIN B. (1998): The possible role of the immune system in Alzheimer's disease. *Exp. Gerontol.*, **33**, 871–881.
22. MCGEER E. G. and MCGEER P. L. (1998): The importance of inflammatory mechanisms in Alzheimer's disease. *Exp. Gerontol.*, **33**, 371–378.
23. MCGEER P. L., AKIYAMA H., ITAGAKI S. and MCGEER E. G. (1989): Activation of the classical complement pathway in brain tissue of Alzheimer patients. *Neurosci. Lett.*, **107**, 341–346.
24. MCGEER P. L., KAWAMATA T., WALKER D. G., AKIYAMA H., TOOYAMA I. and MCGEER E. G. (1993): Microglia in degenerative neurological disease. *Glia*, **7**, 84–92.
25. MCGEER P. L. and MCGEER E. G. (1995): The inflammatory response system of brain. Implications for therapy of Alzheimer and other neurodegenerative diseases. *Brain Res. Rev.*, **21**, 195–218.
26. MEDA L., CASSATELLA M. A., SZENDREI G. I., OTVOS L. JR., BARON P., VILLALBA M., FERRARI D., and ROSSI F. (1995): Activation of microglial cells by  $\beta$ -amyloid protein and interferon  $\gamma$ . *Nature*, **374**, 647–650.
27. MOENNING U., SANDBRINK R., BANATI R. B., MASTERS C. L. and BEYREUTHER K. (1994): Transforming growth factor beta mediates increase of mature transmembrane amyloid precursor protein in microglial cells. *FEBS Lett.*, **342**, 267–272.
28. MOENNING U., SCHREITER-GASSER U., HILBICH C., BUNKE D., PRIOR R., MASTERS C. and BEYREUTHER K. (1991): Alzheimer amyloid  $\beta$ /A4 protein-reactive antibodies in human sera and CSF. In IQBAL K., MCLACHLAN D., WINBLAD B. and WISNIEWSKI H.: Alzheimer's disease. Biology, diagnosis and therapeutics. John Wiley & Sons, Chichester, 557–776.
29. PARESE D. M., GHOSH R. N. and MAXFIELD F. R. (1996): Microglial cells internalize aggregates of the Alzheimer's disease amyloid  $\beta$ -protein via a scavenger receptor. *Neuron*, **17**, 553–565.
30. PERCY M. E. (1993): Peripheral biological markers as confirmatory or predictive tests for Alzheimer disease in the general population and in Down syndrome. In BERG J. M., KARLINSKY H. and HOLLAND A. J.: Alzheimer disease, Down syndrome, and their relationship. University Press, Oxford–New York–Tokyo–Toronto, 199–223.
31. ROGERS J., COOPER N. R., WEBSTER S., SCHULTZ J., MCGEER P. L., STYREN S. D., CIVIN W. H., BRACHOVA L., BRADT B. and WARD P. (1992): Complement activation by  $\beta$ -amyloid in Alzheimer's disease. *Proc. Natl. Acad. Sci. USA*, **89**, 10016–10020.
32. ROZEMULLER J. M., EIKELENBOOM P., STAM F. C., BEYREUTHER K. and MASTERS C. L. (1989): A4 protein in Alzheimer's disease. Primary and secondary cellular events in extracellular amyloid deposition. *J. Neuropathol. Exp. Neurol.*, **48**, 674–691.
33. SCHMITT T. L., STEGER M.-M., PAVELKA M. and GRUBECK-LOEBENSTEIN B. (1997): Interactions of the Alzheimer  $\beta$  amyloid fragment (25–35) with peripheral blood dendritic cells. *Mech. Ageing Dev.*, **94**, 223–232.
34. SCHMITT T., STEINER E., KLINGLER P., SZTANKAY A. and GRUBECK-LOEBENSTEIN B. (1996): The production of an amyloidogenic metabolite of the Alzheimer amyloid  $\beta$  precursor pro-

- tein (APP) in thyroid cells is stimulated by interleukin 1 $\beta$ , but inhibited by interferon gamma. *J. Clin. Endocrinol. Metab.*, **81**, 1666–1669.
35. SCHWARZMAN A. L., GREGORI L., VITEK M. P., LYUBSKI S., STRITTMATTER W. J., ENGHILDE J. J., BHASIN R., SILVERMAN J., WEISGRABER K. H., COYLE P. K., ZAGORSKI M. G., TALAFIOUS J., EISENBERG M., SAUNDERS A. M., ROSES A. D. and GOLDGABER D. (1994): Transthyretin sequesters amyloid  $\beta$  protein and prevents amyloid formation. *Proc. Natl. Acad. Sci. USA*, **91**, 8368–8372.
  36. SELKOE D. J. (1994): Cell biology of the amyloid beta-protein precursor and the mechanism of Alzheimer's disease. *Annu. Rev. Cell Biol.*, **10**, 373–403.
  37. SELKOE D. J. (1994): Normal and abnormal biology of the  $\beta$ -amyloid precursor protein. *Annu. Rev. Neurosci.*, **17**, 489–517.
  38. SEUBERT P., VIGO-PELFREY C., ESCH F., LEE M., DOVEY H., DAVIS D., SINHA S., SCHLOSSMACHER M. G., WHALEY J., SWINDLEHURST C., MCCORMACK R., WOLFERT R., SELKOE D. J., LIEBERBURG I. and SCHENK D. (1992): Isolation and quantification of soluble Alzheimer's  $\beta$ -peptide from biological fluids. *Nature*, **359**, 325–327.
  39. SHAFFER L. M., DORITY M. D., GRUPTA-BAUSAL R., FREDERICKSON R. C., JOUKIN S. G. and BRUNDEN K. R. (1995): Amyloid  $\beta$  protein removal by neuroglial cells in culture. *Neurobiol. Aging*, **16**, 737–745.
  40. SINGH V., FUDENBERG H. and BROWN F. (1987): Immunologic dysfunction. Simultaneous study of Alzheimer's and older Down's patients. *Mech. Ageing Dev.*, **37**, 257–264.
  41. SINGH V. K. (1997): Neuroautoimmunity: Pathogenic implications for Alzheimer's disease. *Gerontology*, **43**, 79–94.
  42. SNOW A. D., MAR H., NOCHLIN D., KIMATA K., KATO M., SUZUKI S., HASSELL J. and WIGHT T. N. (1988): The presence of heparan sulfate proteoglycans in the neuritic plaques and congophilic angiopathy in Alzheimer's disease. *Am. J. Pathol.*, **133**, 456–463.
  43. STRITTMATTER W. J. and ROSES A. D. (1995): Apolipoprotein E and Alzheimer disease. *Proc. Natl. Acad. Sci. USA*, **92**, 4725–4727.
  44. THEYER G., KRAMER G., ASSMANN I., SHERWOOD E., PREINFALK W., MARBERGER M., ZECHNER O. and STEINER G. E. (1992): Phenotypic characterization of infiltrating leukocytes in benign prostatic hyperplasia. *Lab. Invest.*, **66**, 96–107.
  45. TOKUDA T., FUKUSHIMA T., IKEDA S., SEKIJIMA Y., SHOJI S., YANAGISAWA N. and TAMAOKA A. (1997): Plasma levels of amyloid  $\beta$  proteins A $\beta$  1–40 and A $\beta$  1–42(43) are elevated in Down's syndrome. *Ann. Neurol.*, **42**, 271–273.
  46. TRIEB K., RANSMAYR G., SGONC R., LASSMANN H. and GRUBECK-LOEBENSTEIN B. (1996): APP peptides stimulate lymphocyte proliferation in normals, but not in patients with Alzheimer's disease. *Neurobiol. Aging*, **17**, 541–547.
  47. VASILAKOS J., CARROLL R. and EMMERLING M. (1994): Interleukin 1 $\beta$  dissociates  $\beta$ -amyloid precursor protein and  $\beta$ -amyloid peptide secretion. *FEBS Lett.*, **354**, 289–292.
  48. VASSALLI P. (1992): The pathophysiology of tumor necrosis factor. *Annu. Rev. Immunol.*, **10**, 411–452.
  49. WALKER D. G., KIM S. U. and MCGEER P. L. (1995): Complement and cytokine gene expression in cultured microglial derived from postmortem human brains. *J. Neurosci. Res.*, **40**, 478–493.
  50. WEKERLE H., LININGTON C., LASSMANN H. and MEYERMANN R. (1986): Cellular immune reactivity within the CNS. *Trends Neurosci.*, **9**, 171–177.
  51. WYSS-CORAY T., MASLIAH E., MALLORY M., MCCONLOGUE L., JOHNSON-WOOD K., LIN C. and MUCKE L. (1997): Amyloidogenic role of cytokine TGF- $\beta$ 1 in transgenic mice and in Alzheimer's disease. *Nature*, **389**, 603–606.

Received in January 1999

Accepted in April 1999