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Glial Cell Extracellular Matrix in Alzheimer's Disease

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ABSTRACT

Many studies have yielded conflicting results regarding the toxicity of Aβ, the peptide which is the principal component of senile plaques in brains of patients with Alzheimer's disease. Using *in vitro* and *in vivo* models, we have studied the role of glial cells and extracellular matrix molecules in mediating the effects of Aβ. Glial cells respond to Aβ substrate by accumulating and depositing chondroitin sulfate proteoglycans (CSPGs) which are inhibitory to neurite outgrowth. CSPGs are present around the senile plaque core, an area with both dystrophic neurites and a general decrease in normal neurites. We suggest that CSPG may contribute to the pathology by leading to regenerative failure of neurites surrounding senile plaques.

ASTROCYTIC REACTION TO BRAIN INJURY

Generalized Gliosis

Classical observations by Cajal in the early part of this century described the changes associated with astrocytes following trauma and diseases of the CNS.[1] This became known as gliosis and can be defined as the

response of glia to local injury with a characteristic change in morphology of the responding cells. Such reactive cells assume ramified processes and develop pronounced hypertrophy and hyperplasia.[2,3] However, astrocytic response to injury is somewhat heterogeneous. For instance, following a penetrating injury to the cerebral cortex, astrocytes proximal and distal to the lesion demonstrate elevated levels of glial fibrillary acidic protein and therefore are defined as gliotic.[4] However, astrocytes closer to the site of injury are phenotypically different to those that are more distal. Astrocytes surrounding a penetrating injury in the cortex exhibit hyperplasia as well as hypertrophy, whereas astrocytes away from the injury site show almost exclusively hypertrophy.[5,6] Moreover, it has been shown that only the astrocytes surrounding the actual injury site express vimentin, and markers which suggest these cells are undergoing localized proliferation.[6]

It is generally believed that reactive gliosis is the main impediment to the regenerative efforts of the adult mammalian CNS.[7] Such a view is supported by the experiments of Aguayo and collaborators who demonstrated that mature neurons of the CNS retain the ability to regrow so long as the environment contains elements which provide a favorable substrate and support the growth of neuronal processes. However, outgrowth will not occur if the environment presented to the regenerating axonal process is non-permissive or contains actively inhibitory elements. In such a way, regenerating CNS neurons can extend axons into the regeneration-promoting areas of peripheral nerve grafts, but fail to penetrate into the regions where reactive gliosis forms a glial scar.[8–12]

Production of ECM Proteins

While it is established that the cells and matrices of glial scars represent a barrier to axon regeneration, it is still controversial whether it is the cells themselves or molecules of the extracellular matrix which prevent process outgrowth. Glial scars[13] consist of a dense meshwork of hypertrophied astrocytic processes and their associated molecular matrices[13–15] which together present a tortuous path for migrating growth cones. Although the physical presence of the glial scar creates a mechanical barrier that limits axon growth, changes in the molecular

properties of reactive astrocytes associated with a scar could also contribute to regenerative failure.[16] A decrease in growth promoting molecules[17,18] or a local upregulation of axon inhibitory molecules by glia[19] could also diminish regeneration. Many molecules of the extracellular matrix play important roles during development of the nervous system and in homeostatic control of the CNS.[20,21] Synthesis and modification of extracellular matrix components by reactive glial cells may be one of the most important features of the response of the CNS to injury and disease.

Astrocytes respond to wounds in the central nervous system by the production of growth factors and various ECM proteins. In addition, microglia, in regions of neurodegeneration, secrete IL-1[22] which can induce TGFβ production and possibly ECM accumulation by astrocytes.[23] Tenascin and laminin are among several glycoproteins increased at wound sites.[24] Laminin in particular is one of the most potent neurite outgrowth promoting molecules that exists. Tenascin can be both growth promoting or growth inhibiting depending on the presence of associated molecules.[25] Even though the glial scar produces these and other factors that could encourage regeneration, nevertheless, it remains an obstacle to neurite outgrowth. Perhaps, the presence of growth inhibitory molecules can negate the facilitory effects of these factors.

Many believe that astrocytes respond to mechanical wounds through the formation of a glial scar in order to re-establish a compromised glial limitans. Proteoglycans are a major component of the glial limitans and it has been demonstrated that proteoglycans are markedly increased in regions of reactive gliosis due to trauma.[19,26,27] *In vitro* experiments have shown that proteoglycans can be potent inhibitors of neurite outgrowth.[28,29] Thus, their enhanced presence in the glial scar could play a major role in regenerative failure. This same kind of "walling off" response by astrocytes also appears to occur around SPs in AD.

Glial Cells Associated with Senile Plaques in AD

Senile plaques consist of a dense core of amyloid β-protein (Aβ), a 40–42 amino acid peptide derived from a larger precursor, βPP.[30] Microglial cells are found throughout the senile plaque. The specific role of microglia is unknown although they might be responsible for Aβ

generation from βPP. Others have suggested a more active role through the generation of complement attack complexes.[31] Surrounding the Aβ core are many dystrophic neurites and processes of reactive astrocytes. Presumably, the cause of astrocyte reactivity is the extensive neuronal death which occurs throughout the AD brain or their reaction to Aβ. However, a more active role for astrocytes has generally been overlooked[32] and indeed, astrocytes could contribute to the pathology of the disease by altering the local environment to one that compromises neuronal viability.

GLIAL REACTION TO AMYLOID β-PROTEIN (Aβ)

In Vitro Studies

The finding that Aβ is normally produced and is found in a soluble form[33] came as a surprise to many researchers who viewed Aβ as an unwanted, toxic, insoluble byproduct resulting from aberrant proteolysis. Therefore, the key event in SP formation may not be the generation of Aβ per se, but rather factors that promote the accumulation of Aβ. The cellular responses to Aβ are presently being defined and many conflicting studies have shown that Aβ is toxic or trophic to neurons depending on the experimental conditions.[34,35] Much of the confusion of Aβ toxicity may be the result of parameters and factors other than Aβ. Aβ may not have a direct effect on neurons; instead, it may act indirectly by affecting other cells or inducing the accumulation of other molecules which are themselves harmful to neurons. Our approach has been to determine whether glial cells may be involved and whether molecules secondary to Aβ may affect neurons.

In an *in vitro* model[36] Aβ is bound to specific areas on a tissue culture dish and used as a substrate for cells. Since Aβ in the SPs is insoluble, substrate bound Aβ may simulate SP-Aβ better than Aβ added to culture media. Neurons show a preferential adherence to Aβ and laminin together over laminin alone, corroborating another report suggesting that Aβ enhances the growth promoting activity of laminin.[37] Astrocytes, on the other hand, change morphology, become highly motile, and

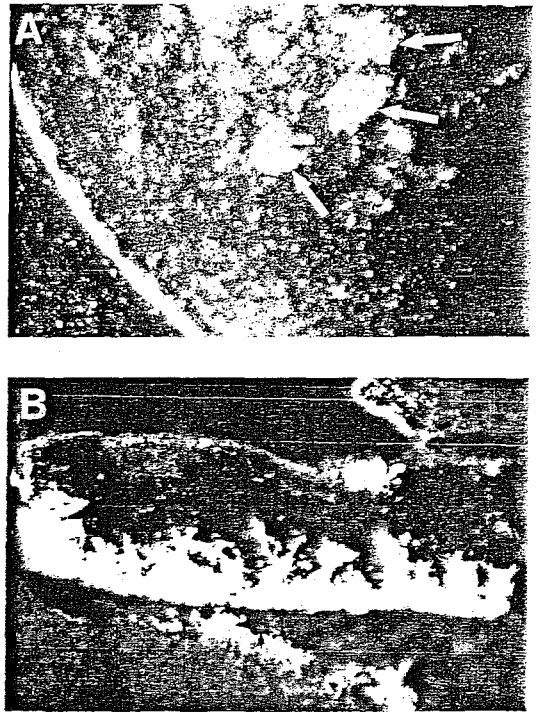

Fig. 13.1 **A.** Astrocytes (arrows) grown on Aβ and laminin substrate accumulate and deposit chondroitin sulfate proteoglycan as indicated by fluorescent antibodies. **B.** Astrocytes infiltrate a nitrocellulose filter implanted in a neonatal rat. Here, the filter was coated with Aβ prior to implantation. The astrocytes are immunoreactive for chondroitin sulfate proteoglycan.

eventually move off the Aβ substrate. Astrocytes in contact with the Aβ substrate accumulate CSPGs and deposit them on the substrate. When astrocytes are allowed to "precondition" the Aβ substrate with CSPG, the substrate becomes inhibitory to neurite growth. This inhibition can be removed by digestion with chondroitinase, an enzyme which degrades chondroitin glycosaminoglycan chains. Therefore, inhibition of neurite

outgrowth is correlated with the presence of CSPG as demonstrated in other systems.[19,28,29]

In Vivo Studies

Previous studies have examined the role of Aβ injected into the brains of animals.[35] Some have found neurodegeneration while others have not, further confounding the controversy of Aβ toxicity. One of the difficulties in interpreting such data is the variable amount of trauma which results from minor differences in the penetrating wounds. While one group found that Aβ injection with proteoglycans yielded fibrillar Aβ which persisted, clear neurodegeneration due to Aβ remains questionable in view of the compounding effects of trauma and the formation of a glial scar.[38]

In one model of glial scarring, nitrocellulose filter implants are inserted into rat cortex. Astrocytes infiltrate the filter, and become intensely GFAP-positive.[16] If the injury was made in an adult animal, these astrocytes accumulated CSPG which inhibits neurite outgrowth.[19] In a neonatal animal on the other hand, astrocytes infiltrate the filter, are GFAP-positive, but do not accumulate CSPG. Further, in the young animal, neurite outgrowth is possible and there is no glial scar formed. Since neonatal animals have astrocytic reaction without all of the characteristics of trauma, we implanted filters which were coated with Aβ to determine the response of these cells. In the presence of Aβ, neonatal astrocytes accumulate CSPG much the same as in the adult animal. While neurodegeneration was not observed in the young animal, it is interesting that Aβ causes young astrocytes to react as if they were adult.

CSPGs have been shown to accumulate at sites of injury in the adult central nervous system.[19,27] While a variety of unknown triggers may be involved in the initiation and maintenance of reactive gliosis and CSPG accumulation, it appears that Aβ may be one such trigger. In the glial scar model of neonates, the presence of Aβ may accelerate, or amplify a normal cellular response. In the adult animal, it has been shown that βPP is increased in response to injury.[39] It is intriguing to consider the possibility that βPP expression could yield Aβ which in turn induces CSPG at injury sites. Therefore, one difference between the adult and young animal may be βPP expression or processing. Exogenous Aβ in the

neonate may overcome any difference in βPP and result in the same response of the adult, namely CSPG accumulation. This "normal" response could be increased or more pronounced with aging, thus explaining the presence of CSPG in adult wounds without exogenous Aβ.

Astrocytes in Several Neurodegenerative Diseases Contain CSPG

As noted earlier, many neurodegenerative diseases display reactive glia as an aspect of the pathology. Previously, we demonstrated that GFAP positive astrocytes in cases of Alzheimer's disease also contain CSPG.[36,40] The colocalization is especially noticed in the vicinity of SPs, consistent with *in vitro* and *in vivo* models of CSPG deposition upon an insoluble Aβ substrate. This observation suggests that Aβ may be responsible for the accumulation of CSPG. We wanted to determine whether CSPG accumulation by reactive astrocytes is specific to Alzheimer's disease, or if it is common to other conditions of gliosis.

Recently, we demonstrated that reacting astrocytes in several neurodegenerative diseases contain CSPG.[41] While the study focused on diseases characterized by neuronal inclusions such as Parkinson's disease, Pick's disease, diffuse Lewy body disease, and progressive supranuclear palsy, we also examined cases of Huntington's disease. None of these diseases are charactierized by SPs or Aβ deposition; however, all of them have CSPG-positive astrocytes. Of particular interest was Huntington's disease, which has CSPG-containing astrocytes in the basal gangalia but not in the cortex, suggesting astrocytic CSPG is associated with neurodegeneration.

While Aβ may play a key role in CSPG deposition in AD, there may be other initiators for CSPG accumulation during neurodegeneration. An important difference between astrocytic CSPG accumulation in AD and the other neurodegenerative diseases may be deposition. CSPG immunoreactivity in the other diseases is confined to the astrocyte itself and may represent an internal accumulation or accumulation very close to the surface of the cell. In AD, on the other hand, CSPG is deposited around the SPs. This corresponds with the *in vitro* model which indicates that Aβ induces CSPG accumulation *and* deposition. The release and

deposition of CSPG may have significant impact on the neuronal environment in the periphery of senile plaques.

ENVIRONMENT OF THE SENILE PLAQUE PERIPHERY

Extracellular Matrix Proteins Associated with Senile Plaques of Alzheimer's Disease

Increases in specific glycosaminoglycans were initially reported in extracts made from the brains of Alzheimer's disease patients.[42] Later, use of cationic dyes such as Alcian blue showed that glycosaminoglycans are associated with senile plaques (SP).[43] Further experimental approaches using a basic fibroblast growth factor (bFGF) binding assay indicates heparan sulfate proteoglycans (HSPG) in amyloid deposits, dystrophic neurites around SPs and extracellular NFTs.[44,45] Immunocytochemical experiments indicate that the HSPG in SPs may be perlecan, the basement membrane HSPG.[46] Chondroitin sulfate proteoglycans show a different distribution than HSPG.[40] While HSPG is found throughout the SP, CSPG is found only in the periphery, surrounding the Aβ core. CSPG is also present in intracellular NFTs and dystrophic neurites as well as reactive astrocytes in the vicinity of senile plaques.[36] Dermatan sulfate proteoglycan is also present in the SP periphery.[47]

In addition to proteoglycans, several other ECM proteins are found in SPs including fibronectin,[48] laminin,[49] and collagen type IV.[49] These ECM molecules are neurite outgrowth promoting molecules, and were hypothesized to promote neurite outgrowth and sprouting in the SP. Indeed, several studies report increased and aberrant sprouting of neurites in SPs. These findings support the idea of trophic effects of Aβ and localization of growth factors in the SP.

ECM-related molecules are also present in SPs including proteases and protease inhibitors that are involved in the degradation and protection of ECM molecules. α1-antichymotrypsin, α1-antitrypsin, anti-thrombin III, protease nexin I, and other protease inhibitors have been identified.[50] Proteases including trypsin,[51] chymotrypsin,[52] and

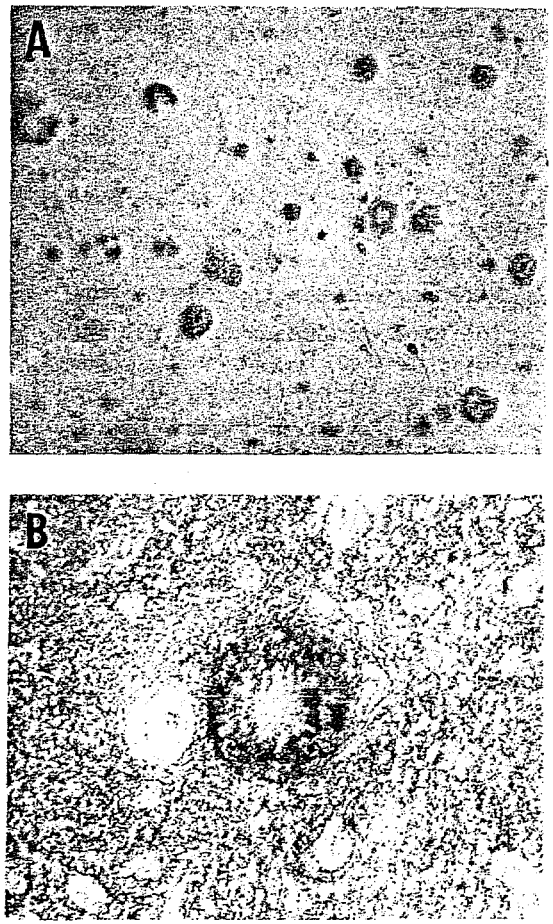

Fig. 13.2 **A.** bFGF binds to heparanase sensitive sites in senile plaques of Alzheimer's disease. **B.** Chondroitin 6-sulfate proteoglycan is found in the periphery, surrounding the Aβ core.

metalloprotease 9[53] have also been localized to SP. One recent hypothesis suggests that a proteolytic imbalance occurs in the area of a SP.[54] The accumulation of ECM proteins in SPs might be the result of decreased matrix turnover. Indeed, the presence of TGFβ[55] in SPs could

upregulate ECM molecules and protease inhibitors, while down-regulating matrix proteases.

Degenerating Neurites

Surrounding the Aβ core of the SP are swollen, tortuous neuronal processes called dystrophic neurites. These neurites contain τ,[56] ubiquitin,[57] and show an accumulation of βPP,[58,59] the precursor protein which generates Aβ. The exact cause of neuritic dystrophy is unknown; however, it seems likely that a factor or event in the senile plaque is responsible, since these lesions are focal. It has long been hypothesized that Aβ itself is the cause of neuritic dystrophy; however, numerous studies have called this hypothesis into question especially in light of the Aβ toxic/trophic debate.

The area surrounding SPs has been shown to lack normal neurites.[60] Using neurofilament antibodies, Benes[60] demonstrated that the density of normal neurites was reduced around SPs. Reduced neurite density occurred not only in the Aβ core as would be expected but also up to two plaque core distances away. Surprisingly, some normal neurites curve around the SP periphery. This suggests that the SP environment, in addition to causing neuritic dystrophy, may somehow prevent or reduce normal neurites in this area.

Neuronal Sprouting?

Another hypothesis for the cause of neuritic dystrophy is aberrant sprouting of neurons.[61] Many growth factors and growth promoting molecules have been found in SPs including bFGF,[62] laminin and collagen. Growth associated proteins such as GAP43[63] and NTP[64] have been identified in neurites of SPs. While it has been suggested that excessive or abnormal sprouting of neurites due to increased trophism may cause neuritic dystrophy, the relation of these molecules to regeneration has not been overlooked.[65] Indeed, GAP43 and the other growth promoting/associated molecules are all characteristic of wound or regeneration related molecules.

This suggests a different view of the neurites and ECM proteins in SPs. Instead of a growth promoting, trophic environment for excessive neurite outgrowth, the SP may *prevent* the restoration of synapses by

inhibiting neuritic infiltration into the area. Such an idea is supported by the bulbous, dystrophic neurites found in Aβ deposits of AD brain which differ from degenerating neurites found in other neurological conditions[66] and are not characterized by large, focal, extracellular deposits of wound related molecules.

Why is there a Halo?

Further evidence suggests that the periphery around the SP, rather than the core itself, has the greatest impact on neurons. When retinal ganglion cells are grown on cryostat sections of AD brain[67] they attach and put forth processes. No difference in the density of neurons which attach to SP cores and those which attach to areas lacking SPs is noted. However, the number which adhere to the periphery of SPs was substantially decreased. In addition, growth in this peri-plaque region is inhibited and neurons are more likely to extend a process away rather than toward SPs. Some neurons were observed which initially grow toward a SP but then curve and turn away. These results are consistent with the observations of a lack of normal neurites in the periphery of SPs.

As neurons die throughout the brain in AD, there may be an attempt to recover some of the lost synapses through collateral sprouting. Astrocytic deposition of CSPG may impact this process by inhibiting neurite outgrowth, thus preventing the sprouts from reaching their potential targets. Therefore, while the number of synapses, neurons, and neurite density decreases throughout the brain in AD, attempts at recovery are possible except in the area of the periphery of the SP where CSPG prevents neuritic outgrowth as well as synaptic restoration. Synapse loss is accentuated in SPs, but not in diffuse SPs where there is no distinction from the rest of the neuropil.[68] Interestingly, diffuse SPs do not have CSPG accumulation. Therefore, the presence of CSPG is correlated with increased synaptic pathology in the AD brain.

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REFERENCES

1. Cajal RS. *Degeneration and Regeneration of the Nervous System.* New York: Hafner; 1928.
2. Lindsay RM. In: *Astrocytes.* Orlando: Academic Press, pp. 231–262, 1986.
3. Reier PJ. In: *Astrocytes.* Orlando: Academic Press, pp. 263–324, 1986.
4. Singh DN and Mathew TC. *Acta Anat. Basel.* 1989; **134**:156–159.
5. Takamiya Y, et al. *Brain Res.* 1988; **466**:201–210.
6. Schiffer D, et al. *Int. J. Dev. Neurosci.* 1993; **11**:269–280.
7. Reier PJ and Houle JD. *Adv. Neurol.* 1988; **47**:87–138.
8. Aguayo AJ, David S and Bray GM. *J. Exp. Biol.* 1981; **95**:231–240.
9. David S and Aguayo AJ. *Science.* 1981; **214**:931–933.
10. Benfey M and Aguayo AJ. *Nature.* 1982; **296**:150–152.
11. Aguayo AJ, et al. *Neurosci. Lett.* 1984; **45**:53–58.
12. David S and Aguayo AJ. *J. Neurocytol.* 1985; **14**:1–12.
13. Reier PJ, Stensaas LJ and Guth L. In: *Spinal Cord Reconstruction.* New York: Raven Press, pp. 163–195, 1983.
14. Maxwell WL, et al. *Philos. Trans. R. Soc. Lond. [Biol].* 1990: **328**:479–500.
15. Maxwell WL, et al. *Philos. Trans. R. Soc. Lond. [Biol].* 1990; **328**:501–513.
16. Rudge JS and Silver J. *J. Neurosci.* 1990; **10**:3594–3603.
17. Snider WD and Johnson EM. *Ann. Neurol.* 1989; **26**:489–506.
18. Smith GM, et al. *Dev. Biol.* 1990; **138**:377–390.
19. McKeon RJ, et al. *J. Neurosci.* 1991; **11**:3398–3411.
20. Bignami A, Asher R and Perides G. *Adv. Exp. Med. Biol.* 1991; **296**:197–206.
21. Celio MR and Blumcke I. *Brain Res. Rev.* 1994; **19**:128–145.
22. Giulian D, et al. *J. Neurosci.* 1988; 8:709–714.
23. Da Cuhna A, et al. *J. Neurochem.* 1993; **42**:71–86.
24. Brodkey JA, et al. *Exp. Neurol.* 1993; **123**:251–270.
25. Fraisner A and Kruse J. *Neuron.* 1990; 5:627–637.
26. Pindzola RR, Doller C and Silver J. *Dev. Biol.* 1993; **156**:34–48.
27. Bovolenta P, Wandosell F and Nieto-Sampedro M. *Eur. J. Neurosci.* 1993; 5:454–465.
28. Snow DM, et al. *Exp. Neurol.* 1990; **109**:111–130.
29. Snow DM and Letrourneau PC. *J. Neurobio.* 1992; **23**:322–336.
30. Kang J, et al. *Nature.* 1987; **325**:733–736.
31. McGeer PL, et al. *Glia.* 1993; 7:84–92.
32. Fredrickson RCA. *Neurobiol. Aging.* 1992; **13**:2485–2490.
33. Shoji M, et al. *Science.* 1992; **258**:126–129.
34. Podlinsny MB, et al. *Am. J. Path.* 1993; **142**:17–23.
35. Special Issue. *Neurobiol. Aging.* 1992; 13 (5).
36. Canning DR, et al. *Exp. Neurol.* 1993; **124**:289–298.
37. Koo EH, Park L and Selkoe DJ. *Proc. Natl. Acad. Sci. USA.* 1993; **90**:4748–4752.

38. Snow AD, et al. *Neuron.* 1994; 12:219–234.
39. Otsuka N, Tomonaga M and Ikeda K. *Brain Res.* 1991; 568:335–338.
40. DeWitt DA, et al. *Exp. Neurol.* 1993; 121:149–152.
41. DeWitt DA, et al. *Brain Res.* 1994 (in press).
42. K. Suzuki, R. Katzman and Korey SR. *J. Neuropathol. Exp. Neurol.* 1965; 24:211–224.
43. Snow AD, Willmer JP and Kisilevsky R. *Human Path.* 1987; 18:505–510.
44. Perry G, et al. *J. Neurosci.* 1991; 11:3679–3683.
45. Siedlak SL, et al. *J. Histochem. Cytochem.* 1991; 39:899–904.
46. Snow AD, et al. *Amer. J. Path.* 1990; 137:1253–1270.
47. Snow AD, et al. *J. Histochem. Cytochem.* 1992; 40:105–113.
48. Howard J and Pilkington GJ. *Neurosci. Lett.* 1990; 118:71–76.
49. Perlmutter LS, et al. *J. Neurosci. Res.* 1991; 30:673–681.
50. Kalaria RN. *Clinical Neurosci.* 1993; 1:204–211.
51. Smith MA, Kalaria RN and Perry G. *Biochem. Biophys. Res. Com.* 1993; 193:579–584.
52. Smith MA, et al. *J. Neuropath. Exp. Neurol.* 1993; 52:303.
53. Lim GP, et al. *Soc. Neurosci. Ab.* 1993; 19:195.
54. Smith MA and Perry G. *Medical Hypothesis.* 1994; 42:277–279.
55. van der Wal EA, Gomez-Pinilla F and Cotman CW. *Neuroreport.* 1993; 4:69–72.
56. Grundke-Iqbal I, et al. *Proc. Natl. Acad. Sci. USA.* 1986; 85:4506–4510.
57. Perry G, et al. *Proc. Nail. Acad. Sci. USA.* 1987; 84:3033–3036.
58. Cras P, et al. *Proc. Natl. Acad. Sci. USA.* 1991; 88:7552–7556.
59. Kawai M, et al. *Am. J. Path.* 1992; 140:947–958.
60. Benes FM, et al. *Neurosci.* 1991; 42:651–660.
61. Gedes JW, Anderson KJ and Cotman CW. *Exp. Neurol.* 1986; 94:767–776.
62. Gomez-Pinilla F, Cummings BJ and Cotman CW. *Neuroreport.* 1990; 1:211–214.
63. Masliah E, et al. *Brain Res.* 1992; 574:312–316.
64. de la Monte SM and Wands JR. *J. Neurol. Sci.* 1992; 113:152–164.
65. Masliah E, et al. *Neuron.* 1991; 6:729–739.
66. Benzing WC, Mufson EJ and Armstrong DM. *Brain Res.* 1993; 606:10–18.
67. Carpenter MK, Crutcher KA and Kater SB. *Neuobiol. Aging.* 1993; 14:207–215.
68. Masliah E, et al. *Am. J. Pathol.* 1990; 137:1293–1297.

14 Role of Inflammation and Complement Activation in Alzheimer's Disease

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ABSTRACT

A variety of inflammatory proteins has been identified, particularly in the vicinity of β-amyloid plaques, in the brain of patients with Alzheimer's disease. Current findings indicate that these molecules are involved in a number of key steps in the pathological cascade. Activation products of classical complement pathway Clq, C4 and C3, but not the alternative pathway factor properdin, have been demonstrated in diffuse and classical plaques. In addition, complement receptors (CR3 and CR4) bearing cells are found within classical plaques. There are contradictory findings about the question whether or not the late complement proteins that can form the membrane attack complex, are present in Alzheimer's disease brains.

In this chapter we review the findings indicating that complement activation in amyloid plaques does not proceed further than C3. The idea is discussed that in Alzheimer's disease, complement does not function as an inflammatory mediator through membrane attack complex formation, but through the action of early complement activation products.