Amyloid beta, TNFα and FAIM-L; approaching new therapeutic strategies for AD

Paulina Carriba1,2,3* and Joan X. Comella1,2,3

1 Institut de Recerca de l’Hospital Universitari de la Vall d’Hebron (VHIR), Barcelona, Spain
2 Facultat de Medicina, Departament de Bioquímica i Biologia Molecular, Institut de Neurociències, Universitat Autònoma de Barcelona, Bellaterra, Spain
3 Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Spain

*Correspondence: paulina.carriba@gmail.com

Edited by:
Angel Cedazo-Minguez, Karolinska Institutet, Sweden

Reviewed by:
George Perry, University of Texas at San Antonio, USA
Laura Mateos, Karolinska Institutet, Sweden
Maria Ramirez, University of Navarra, Spain

Keywords: soluble amyloid beta, TNFα, neuroinflammation, neurodegeneration, FAIM-L

A commentary on

Successful therapies for Alzheimer’s disease: why so many in animal models and none in humans?
by Franco R, Cedazo-Minguez A. Front Pharmacol (2014) 5:146. doi:10.3389/fphar.2014.00146

The aim of this commentary is to complement the review of Franco and Cedazo-Minguez (1).

ALZHEIMER’S DISEASE AND AMYLOID BETA
Defining characteristics of Alzheimer’s disease (AD) are memory defects, synaptic alterations, presence of neuroinflammatory mediators, and a progressive neurodegeneration. One of the histopathological hallmarks of the disease is the presence of amyloid beta (Aβ) plaques; however, it seems that soluble oligomers, also called Aβ-derived-diffusible-ligands (ADDLs), are the really toxic species involved in the pathogenesis of AD (2). ADDLs are a blend of several sizes of oligomeric Aβ species (3). This suggests that most of the effects on the neurons cannot be attributed to interactions with specific receptors, but rather to interaction and alteration of the proteins and lipids within the cell membranes (4). ADDLs have been detected in AD patients (5), increasing their content with severity (6). Dimers isolated from AD brains impair LTP, enhance LTD, reduce dendritic spines density, and correlate with clinical state (7). Also, they are able to induce hyperphosphorylation of Tau and neuritic dystrophy (8). Soluble oligomers of Aβ are toxic for the neurons (9). They also cause synaptic dysfunction (10) through the activation of caspase-3 (11). Moreover, the inflammatory response characterized by the secretion of various products is initiated by the glial cells when these cells detect Aβ (12). Thus, Aβ appears to be a decisive trigger for the development of this neurodegenerative disorder.

NEUROINFLAMMATION AND NEURODEGENERATION, TWO OF THE CHARACTERS IN THE PROGRESSION OF THE DISEASE
The neuronal loss observed in the AD brains, as occurs in other neurodegenerative diseases, is produced mainly by apoptosis (13, 14). Sustained neuroinflammatory response contributes to the progression of the disease (15, 16), which ultimately it strengthens the neuronal death (17).

For their physiological importance, both processes are highly regulated; consequently, they can be harmful when deregulated. Apoptosis can be initiated through the mitochondria – intrinsic pathway – or by the stimulation of death receptors (DRs) – extrinsic pathway – [see Ref. (18)]. DRs are cell surface receptors that belong to the TNF family. They are able to trigger apoptosis upon ligand binding. DRs and their ligands are expressed physiologically in the brain (19), with important roles in brain development (20, 21) and in cellular homeostasis in adulthood (22). In neurons, in normal conditions, the activation of these receptors does not initiate apoptosis (23, 24). Likewise, inflammation is generally a beneficial physiological response. In fact, it has been described that the initial glial inflammatory response in AD is protective (25, 26).

TNFα IN THE CROSS-ROAD BETWEEN INFLAMMATION AND APOPTOSIS
In brain, TNFα plays a central role in neuroinflammation, apoptosis, and also in the control of the synaptic strength (27, 28). The TNFα gene maps within the class III region of human leukocyte antigen (HLA). Several polymorphisms were detected associated to AD in this region, and systematic meta-analyses concluded that TNFα is a susceptibility gene in the disease (29). High levels of TNFα have been detected in AD patients (30, 31). TNF system has been proposed as a neurotherapeutic target (32), and its role in animal models of AD has been reported (33–35). However, its function in the disease is not clear. It has been described that TNFα is a contributor of the disease (36, 37), although also that it can protect from the Aβ toxicity (38, 39).

TNFα can stimulate two signaling pathways, survival or death (40). The induction of survival pathways depend on NFκB (40) and/or FLIP-L-dependent activation of ERK (41). In normal conditions, TNFα is not toxic for the neurons, indicating that several regulatory proteins prevent the induction of apoptosis at various stages of TNF signaling (42). Expressed exclusively in neurons, the long form of Fas apoptotic inhibitory molecule (FAIM) protein (FAIM-L) is able to regulate the signaling of TNFα. The down-regulation of FAIM-L
sensitizes neurons to death induced by TNFα and also by FAS (43). In Parkinson’s disease, it has been proposed that FAIM-L expression could be reduced in dopaminergic neurons, being then this type of neurons more vulnerable to FAS-induced death (44). We have evidence that ADDLs reduce the expression of FAIM-L. The reduction of FAIM-L changes the response mediated by TNFα against the Aβ toxicity, from protection to a contributor in the neuronal death, thus, accelerating the neurodegenerative process (paper under review).

**NEW PERSPECTIVES IN FINDING POTENTIAL TARGETS**

FAIM-L, modulating the function of the TNFα in neurons, would be an example of target molecule able to ameliorate both neurodegeneration and deleterious neuroinflammation. Although speculative, it is possible to hypothesize that the reduction in the neuronal loss would result in an improvement also in the cognition. Aβ is able to cause all the features observed in the disease, thus, targets able to act in more than one of the aspects of the disease would be more useful. However, this type of strategy only would be effective in the prevention of disease progression rather than in the prevention of the disease. Moreover, whereas we do not have good biomarkers for early detection, it seems difficult that potential AD patients (99% of the cases correspond to the non-familiar or sporadic) without any symptom or diagnosis would take drugs to prevent AD in the future, unless these were supplements or healthy habits. Thus, therapies able to prevent the progression of the disease acquire greater relevance.

**ACKNOWLEDGMENTS**

This work was funded by the Spanish Government’s “Ministerio de Sanidad y Consumo” (CIBERNED grants to Joan X. Comella CB06/05/1104; PI2010/08 and 2013/01); “Ministerio de Economía y Competitividad” (SAF2010-19953 to Joan X. Comella), and by the “Generalitat de Catalunya” (Suport als Grups de Recerca Consolidats 2009SGR346). Paulina Carriba was awarded a “Beatriu de Pinós” postdoctoral grant from the “Generalitat de Catalunya” co-financed by the FP7-People-COFUND Programme.

**REFERENCES**

1. Franco R, Cedazo-Minguez A. Successful therapies for Alzheimer’s disease: why so many in animal models and none in humans? Front Pharmacol (2014) 5:16–6. doi:10.3389/fphar.2014.00016
2. Mc Donald JM, Savva GM, Brayne C, Welzel AT, Forster G, Shankar GM, et al. The presence of sodium dodecyl sulphate-stable Aβ dimers is strongly associated with Alzheimer-type dementia. Brain (2010) 133:1328–41. doi:10.1093/brain/awq065
3. Benilova I, Karran E, De Strooper B. The toxic Aβ oligomer and Alzheimer’s disease: an emperor in need of clothes. Nat Neurosci (2012) 15:349–57. doi:10.1038/nn.3028
4. Campioni S, Mannini B, Zampagni M, Pensalfini A, Parrini C, Evangelisti E, et al. A causative link between the structure of aberrant protein oligomers and their toxicity. Nat Chem Biol (2010) 6:21–7. doi:10.1038/nchembio.283
5. Lacor PN, Buniel MC, Chang L, Fernandez SJ, Gong Y, Viola KL, et al. Sympatic targeting by Alzheimer-related amyloid beta oligomers. J Neurosci (2004) 45:10191–100. doi:10.1523/JNEUROSCI.3432-04.2004
6. Lambert MP, Velasco PT, Chang L, Viola KL, Fernandez S, Lacor PN, et al. Monoclonal antibodies that target pathological assemblies of Aβ. J Neurochem (2007) 100:23–35. doi:10.1111/j.1471-419X.2006.06157.x
7. Shankar GM, Li S, Mehta TH, Garcia-Muñoz A, Shepardson ND, Snider I, et al. Amyloid-β protein dimers isolated directly from Alzheimer’s brains impair synaptic plasticity and memory. Nat Med (2008) 14:837–42. doi:10.1038/nm1782
8. Jin M, Shepardson ND, Yang T, Cheng G, Walsh D, Selkoe DJ. Soluble amyloid beta-protein dimers isolated from Alzheimer’s cerebrospinal fluid induce Tau hyperphosphorylation and neurotic degeneration. Proc Natl Acad Sci U S A (2011) 108:5819–24. doi:10.1073/pnas.1010331108
9. De Felice FG, Velasco PT, Lambert MP, Viola K, Fernandez SJ, Ferreira ST, et al. Aβ oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. J Biol Chem (2007) 282:11590–601. doi:10.1074/jbc.M607483200
10. Walsh DM, Klubyan J, Fadeeva IV, Cullen WK, Amsyl R, Wolfe MS, et al. Naturally-secreted oligomers of amyloid β protein potently inhibit hippocampal long-term potentiation in vivo. Nature (2002) 416:535–9. doi:10.1038/416535a
11. Jo J, Whitcomb DJ, Olsen KM, Kerrigan TL, Lo SC, Bru-Mercier G, et al. (Aβ1-42) inhibition of LTP is mediated by a signaling pathway involving caspase-3, Akt and GSK-3β. J Neurosci (2011) 31:4545–7. doi:10.1523/JNEUROSCI.0528-11.2011
12. Butovsky O, Koronyo-Hamaoui M, Kunis G, Ophir E, Landa G, Cohen H, et al. Glia-tamer acute lights against Alzheimer’s disease by inducing dendritic-like microglia expression insulin-like growth factor 1. Proc Natl Acad Sci U S A (2006) 103:11784–9. doi:10.1073/pnas.0604681103
13. Cotman CW, Anderson AJ. A potential role for apoptosis in neurodegeneration and Alzheimer’s disease. Mol Neurobiol (1995) 10:19–45. doi:10.1007/BF02740836
14. Mattson MP. Apoptosis in neurodegenerative disorders. Nat Rev Mol Cell Biol (2000) 1:118–9. doi:10.1038/35040009
15. Saito K, Winner B, Carson CT, Collier JG, Boyer L, Rosenfeld MG, et al. A Nurr1/COREST pathway in microglia and astrocytes protects dopaminergic neurons from inflammation-induced death. Cell (2009) 137:47–59. doi:10.1016/j.cell.2009.01.038
16. Glass CK, Saito K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. Cell (2010) 140:918–34. doi:10.1016/j.cell.2010.02.016
17. Aktyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer’s disease. Neurobiol Aging (2000) 21:383–421. doi:10.1016/S0197-4580(99)00124-X
18. Wilson NS, Dixit V, Ashkenazi A. Death receptor signal transducers: nodes of coordination in immune signaling networks. Nat Immunol (2009) 10:348–55. doi:10.1038/ni.1714
19. Bette M, Kaut O, Schäfer MK, Weihe E. Constitutive expression of p55TNFR mRNA and mitogen-specific up-regulation of TNFα and p75TNFR mRNA in mouse brain. J Comp Neurol (2003) 465:417–30. doi:10.1002/cne.10705
20. Cheema ZF, Wade SB, Sata M, Walsh K, Sohrabji F, Miranda RC. Fas/Apo [apoptosis]-1 and associated proteins in the differentiating cerebral cortex: induction of caspase-dependent cell death and activation of NF-kappaB. J Neurosci (1999) 19:1754–70.
21. Zollini C, Kielczewski S, Klussmann S, Wengen T, Kenzelmann M, Schreglmann N, et al. Control of neuronal branching by the death receptor death domain (Fas/Apo-1). J Neurosci (2004) 16:2371–9. doi:10.1523/JNEUROSCI.349-04.2004
22. Gerhardt E, Kugler S, Leist M, Beier C, Berlucchi L, Volbracht C, et al. Cascade of caspase activation in potassium-deprived cerebellar granule neurons: targets for treatment with peptide and protein inhibitors of apoptosis. Mol Cell Neurosci (2001) 17:171–37. doi:10.1006/mcne.2001.0962
23. Putcha GV, Harris CA, Moulder KL, Easton RM, Thompson CR, Johnson EM Jr. Intrinsinc and extrinsic pathway signaling during neuronal apoptotic lesions from the analysis of mutant mice. J Cell Biol (2002) 157:441–53. doi:10.1083/jcb.200110108
24. Jimenez S, Baglietto-Vargas D, Caballero C, Moreno-Gonzalez I, Torres M, Sanchez-Varo R, et al. Inflammatory response in the hippocampus of PS1M146LAPP751SL mouse model of Alzheimer’s disease: age-dependent switch in the microglial phenotype from alternative to classi. J Neurosci (2008) 28:11650–61. doi:10.1523/JNEUROSCI.3024-08.2008
25. Boissonneault V, Filali M, Lessard M, Belton J, Wong G, Rivest S. Powerful beneficial effects of macrophage colony-stimulating factor on beta-amyloid deposition and cognitive impairment in Alzheimer’s disease. Brain (2009) 132:1078–92. doi:10.1093/brainawy331
26. Beattie EC, Stellwagen D, Morishita W, Brenneman JC, Ha BK, Von Zastrow M, et al. Control of synaptic strength by glial TNFalpha. Science (2002) 295:2282–5. doi:10.1126/science.1067859
28. Stellwagen D, Malenka RC. Synaptic scaling mediated by glial TNF-alpha. Nature (2006) 440:1054–9. doi:10.1038/nature04671
29. Bertram L, McQueen MB, Mallin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. Nat Genet (2007) 39:17–23. doi:10.1038/ng1934
30. Fillit H, Ding WH, Buee L, Kalman J, Altstiel L, Lawlor B, et al. Elevated circulating tumor necrosis factor levels in Alzheimer’s disease. Neurosci Lett (1991) 129:318–20. doi:10.1016/0304-3940(91)90490-K
31. Tarkowski E, Blennow K, Wallin A, Tarkowski A. Chadwick W, Magnus T, Martin B, Keselman A, He P, Zhong Z, Lindholm K, Berning L, Lee W, Tweedie D, Ferguson RA, Fishman K, Frankola KA. Synaptic scaling and the progression of Alzheimer’s disease. J Neurovirol (2002) 8:529–38. doi:10.1080/10765511.2002.11632334
32. Stellwagen D, Malenka RC. Synaptic scaling of neuroinflammation and Alzheimer’s disease. Front. Neurol. 2014; published online: 18 December 2014. Citation: Carriba P and Comella JX (2014) Amyloid beta, TNF alpha and FAIM-L; approaching new therapeutic strategies for AD. Front. Neurol. 5:276. doi:10.3389/fneur.2014.00276
33. Fillit H, Ding WH, Buee L, Kalman J, Altstiel L, Lawlor B, et al. Elevated circulating tumor necrosis factor levels in Alzheimer’s disease. Neurosci Lett (1991) 129:318–20. doi:10.1016/0304-3940(91)90490-K
34. Barger SW, Hörster D, Furukawa K, Goodman Y, Kriegstein J, Mattson MP. Tumor necrosis factor 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^{2+} accumulation. Proc Natl Acad Sci U S A (1995) 92:9328–32. doi:10.1073/pnas.92.20.9328
35. Saha RN, Ghosh A, Palencia CA, Fung YK, Dudek SM, Pahan K. TNF-alpha preconditioning protects neurons via neuron-specific up-regulation of CREB-binding protein. J Immunol (2009) 183:2068–78. doi:10.4049/jimmunol.0801892
36. Marques-Fernandez F, Planells-Ferrer L, Guillemino R, Gallocan KM, Reix S, Liecha-Canio N, et al. TNFα induces survival through the FLIP-L-dependent activation of the MAPK/ERK pathway. Cell Death Dis (2013) 4:e493. doi:10.1038/cddis.2013.25
37. Hillier S, Woelf CL. Adult neuron survival strategies – slaming on the brakes. Nat Rev Neurol (2004) 5:686–700. doi:10.1038/nrneurol
38. Barger SW, Hörster D, Furukawa K, Goodman Y, Kriegstein J, Mattson MP. Tumor necrosis factor 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^{2+} accumulation. Proc Natl Acad Sci U S A (1995) 92:9328–32. doi:10.1073/pnas.92.20.9328
39. Saha RN, Ghosh A, Palencia CA, Fung YK, Dudek SM, Pahan K. TNF-alpha preconditioning protects neurons via neuron-specific up-regulation of CREB-binding protein. J Immunol (2009) 183:2068–78. doi:10.4049/jimmunol.0801892
40. Micheau O, Tschopp J. Induction of TNF receptor 1-mediated apoptosis via two sequential signaling complexes. Cell (2003) 114:181–90. doi:10.1016/S0092-8674(03)00521-X
41. Marques-Fernandez F, Planells-Ferrer L, Guillemino R, Gallocan KM, Reix S, Liecha-Canio N, et al. TNFα induces survival through the FLIP-L-dependent activation of the MAPK/ERK pathway. Cell Death Dis (2013) 4:e493. doi:10.1038/cddis.2013.25
42. Benn SC, Woelf CL. Adult neuron survival strategies – slaming on the brakes. Nat Rev Neurol (2004) 5:686–700. doi:10.1038/nrneurol
43. Segura MF, Sole C, Pascual M, Moubarak RS, Perez-Garcia MJ, Goszeltino R, et al. The long form of Fas apoptotic inhibitory molecule is expressed specifically in neurons and protects them against death receptor-triggered apoptosis. J Neurosci (2007) 27:11228–41. doi:10.1523/JNEUROSCI.3462-07.2007
44. Yu LY, Saarma M, Arumäe U. Death receptors and caspases but not mitochondria are activated in the GDNF- or BDNF-deprived dopaminergic neurons. J Neurosci (2008) 28:7476–75. doi:10.1523/JNEUROSCI.1877-08.2008

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.