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Hypothesis

Sporadic Alzheimer Disease and That Developing in Down's Syndrome: The Immune System Attacking Self Rather Than Suppressing Infectious Disease Invaders, Toll Like Receptors Triggering Excessive Cytosolic Calcium, Excess Calcineurin Activation, Overexpression of Regulator of Calcineurin1, Runaway Beta-Amyloid Production, Synaptic Loss, Destructive Inflammation and Dementia

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Abstract

Alzheimer Disease may result from excessive stimulation of the innate immune system from development of underlying opportunistic infections and impaired age related self-recognition as non-self, due to immunodeficiency and immunosenescence, resulting in excessive inflammation and runaway Beta-amyloid production (a component of the innate immune system) causing cytosolic calcium overload. Excessive cytosolic calcium may cause over activation of calcineurin and inactivation of cis-trans prolyl isomerase (Pin1), with subsequent loss of dendritic spine maintenance, and synaptic destruction.

Improving immune function, identifying and treating infections, avoiding runaway Beta-amyloid production, inhibiting calcineurin in a manner similar to that utilized in preventing tissue transplant rejection, maintaining the negative feedback loop between regulators of calcineurin1 (RCAN1) and calcineurin, may lead to improved prevention and treatment of Alzheimer Disease and Down's syndrome.

Keywords
Alzheimer's disease; dementia; Down's syndrome; immune; aging; inflammation; infection; synapse; calcineurin; beta-amyloid

1. Introduction

Alzheimer's disease (AD) continues to be a debilitating condition, despite enormous efforts to develop treatments, based primarily on the Beta-Amyloid hypothesis. Further research has indicated the likelihood of infectious disease activation, possibly due to failure of the immune system to recognize foreign invaders, and instead attacks self in ways similar to that which occurs in transplant biology.

Immunosuppression, Immuno-toxicity, immunosenescence and Opportunistic Infections: Opportunistic infections may occur from immune suppression and immune-toxicity due to multiple agents including metal dyshomeostasis, from excess free copper [1], zinc deficiency [2], iron overload [3], aluminum accumulation [4] cytomegalovirus (CMV) encoded interleukin-10 [5], diabetes and obesity [6] which have been noted to be related to AD. Aging, the main risk factor for AD development, is associated with immunosenescence related to declining adaptive immunity involving T and B cells [7]. These abnormalities result in immunosuppression and/or altered immune function [7-12]. Such infections from viruses, bacteria or fungi stimulate Beta-amyloid production in the brain, Beta-amyloid being an anti-microbial peptide and a normal component of the innate immune system [13]. Evidence of viruses, bacteria and fungi have been detected in brains of AD patients, indicating AD may arise in response to infections [14]. Human herpes virus 6A and 7 were identified in AD patients when compared to controls in three independent cohorts dispersed geographically with regulatory relationships between viral abundance and Amyloid Precursor Protein metabolism indicating a viral relationship with molecular, clinical and neuropathological features of AD [15], Cytomegalovirus, Human herpes virus 2, bacteria (including spirochetes and periodontal pathogens such as Porphyromonas gingivalis and Treponema denticola) [5], and fungi [16] have all been identified in AD brain examinations. Porphyromonas gingivalis especially is of interest since it is able to modulate the host immune response through virulence factors facilitating development of chronic periodontitis with involvement of additional oral flora constituents [17]. Modulating the immune response leads to a form of localized immunosuppression in the periodontal region.

P. gingivalis lipopolysaccharide also circulates systemically in more than half of periodontitis patients causing inflammation with higher levels of matrix metalloproteinase-9 [18], metalloproteinase-9 being elevated in AD patients [19]. Beta-amyloid appears to be an antimicrobial peptide, or natural antibiotic produced by the brain in response to infections as a component of the innate immune system [13], rather than a spontaneous development leading to AD. This may be the reason efforts to reduce Beta-amyloid production have not prevented AD. Recurrent or progressive opportunistic infections, especially in a person with some degree of immunosuppression, may lead to increased Beta-amyloid production exceeding clearance. Excessive Beta-amyloid production could lead to loss of anti-microbial function through runaway domain swap, and runaway Beta-amyloid production or other mechanisms of polypeptide

aggregation into a pathogenic Beta-amyloid form [20]. If there are recurrent opportunistic infections in AD brain, reducing or eliminating Beta-amyloid production could possibly even worsen the condition. This is essentially the "Amyloid Protection Hypothesis" of AD, put forward by Tanzi [21] in that Beta-Amyloid is an anciently conserved effector molecule of innate immunity, enabling entrapment of pathogens to protect from infection. Increased levels of brain microbes may stimulate Beta-amyloid production and deposition, leading to inflammation and AD progression[21].

Innate Immune System Activation and Inflammation: Innate immune system activation by recurrent or chronic infections arising due to immunodeficiency activates toll like receptors (TLR), causes acute and chronic inflammation, similar to tissue rejection, as occurs in allogeneic organ transplants. TLR's mobilize intracellular calcium [22], causing calcium dependent calcineurin, to be activated. Calcineurin negatively regulates toll like receptor 2 and 4 activation [23]. Patients on calcineurin inhibitors having a decreased cytokine response to toll like receptor signaling [22]. Excessive Calcineurin activation appears to be an early stage in the pathogenesis of AD and solid organ transplant patients on the calcineurin inhibitor, FK506 had a much lower incidence of AD than expected [24]. ABeta42 also activates calcineurin through post-synaptic signaling, which in turn dephosphorylates (deactivates) Pin1, which maintains dendritic spines [24], leading to loss of synapses as happens in AD. Further validation that calcineurin is involed in Beta-amyloid mediated synaptic loss involves experimental evidence from transgenetically modified plaque bearing mice and wild type mice as well, in which the calcineurin inhibitor, FK-506 (tacrolimus), ameliorated plaque related synaptic loss [25].

Additional features involved with synaptic loss involve complement and microglia, complement possibly being activated by microglia in AD as well, being observed in AD mouse models, since C1q, the initiating protein in classical complement cascade or CR3, the microglial complement receptor interacts with and is necessary for the toxic effects of Abeta oligomers on synapses and hippocampal long term potentiation [26]. Microglia in adult brains engulfs synaptic material involving the microglial complement receptor CR3, when exposed to soluble Abeta. This is suggestive of inappropriate reactivation of developmental pathways in AD, which prune excessive synapses during development, but eliminate essential synapses in AD. Increased expression of beta-amyloid precursor protein APP 695, a specific isoform containing 695 amino acids, does occur during neuronal differentiation of primary hippocampal neurons in a cell culture system, indicating differentiation of neurons is accompanied by increased Beta–APP695 expression and membrane retention of the APP695 protein [27]. The Amyloid Precursor Protein is also a receptor for Slit, a protein involved in axonal guidance during development [28]. This may indicate Beta-Amyloid is moonlighting, or during development, Amyloid precursor protein is involved in neuronal development with axonal guidance, leading to synaptic pruning, which occurs during brain development.

Prefibrillary or oligomeric abeta also appears to induce calcineurin activity, which mediates its effects on neuronal cells [29]. Pathological loss of Pin1 has been found in synapses of AD cortical brain specimens, and in dendritic rafts and post-synaptic density. Pin1 controls cell cycle progression and degrading proteins through the ubiquitin proteasome system, which could result in the accumulation of misfolded Beta-amyloid plaques and hyperphosphorylated tau tangles years, if not decades prior to development of clinical disease as well as altered post synaptic density proteins such as Shank protein involved in organization which would cause distorted

synaptic structures, increased susceptibility to toxicity and impaired synaptic plasticity [30]. Pin1 is a member of a number of a family of molecular chaperones regulating protein folding at proline residues. The microtubule-associated protein, tau, has abundant proline residues. Members of the Peptidyl-prolyl cis/trans isomerase family interact with and regulate tau. Besides Pin1, FK506-binding protein (FKBP) 52, FKBP51, and FKBP12 interact with and regulate tau, which is hyperphosphorylated in AD. Pin1, FKBP52, FKBP12, cyclophilin A, CyclophilinB and CyclophilinD also regulate ABeta production or ABeta toxicity in AD [30]. A cancer related variant of a cell cycle inhibitor gene p21Cip1 is associated with a greater risk of AD [31]. The increased susceptibility to infections in the elderly is mainly due to decreased efficiency of adaptive immunity to suppress microorganisms [32]. Alzheimer patients may also experience a greater degree of immunosenescence than the healthy elderly.

Alzheimer patients have been found to have decreased numbers of CD3+T cells in peripheral blood, when compared to non-demented subjects, the cells themselves exhibiting increased protein oxidation and nitrosative stress when levels of 3-nitrotyrosine are assessed, the proteins being involved in energy metabolism, cytoskeletal structure, intracellular signaling, protein turnover and folding and antioxidant response [33].

Regulator of calcineurin(RCAN1) discovered as a gene on chromosome 21 in Down's syndrome, or Trisomy 21, is overexpressed in Down's syndrome (frequently associated with early onset AD), and also is linked to pancreatic beta-cell dysfunction in type 2 diabetes. Its functions are primarily to inhibit calcineurin and mitochondrial function. Reactive oxygen species, hyperglycemia and other forms of cellular stress cause transient increase in expression. Short term expression causes protective effects through the calcineurin/NFAT pathway, however long term expression over weeks and months causes pathological changes in cells, such as those seen in Down's syndrome, AD, and type 2 diabetes [34]. It's interesting that Beta-amyloid is expressed, not only in the brain, but also the pancreas in type 2 diabetes [35].

2. Conclusions

It appears multiple opportunistic infections in an immune-compromised and/or immunosuppressed state, as well as aberrant innate immune system activation against self rather than non-self, cause excessive stimulation of the innate immune system through TLR's, resulting in excessive if not runaway Beta-amyloid production. Both Beta-amyloid and recurrent infections cause extensive triggering of TLR's on aged neurons, resulting in increased cytosolic Ca^{2+}, calcineurin activation with subsequent loss of Pin1 activity, loss of dendritic spines, synaptic loss, and likely death. Microglia is also likely activated causing widespread excessive inflammation.

Inflammation, neuronal death, and synaptic loss are all features of AD. Efforts to increase immunity and avoid infections may be instrumental in both prevention and treatment of AD. Calcineurin inhibitors, such as FK506, as suggested by O'Neal, et al [24] may be a useful approach in treatment of AD as well, and could be helpful in prevention of synaptic loss from immunosensenescence, or excessive inflammation resulting from the aged immune system attacking self. Immunosensecence leading to a miss-targeted immune system, (permitting infections while attacking self) likely interacts in development of age related diseases such as AD, and other age related conditions. Intervention in multiple aspects of AD development and

progression may be necessary to achieve success, such as reducing pathogenic oral flora, improving overall immunity, and suppressing aberrant immune responses.

Diet may have some role as well, since diets rich in foods containing polyphenols with nuts, soy, citrus, berries, olive oil, tea, leafy vegetables and red wine seem to reduce the chance of developing AD [36]. Polyphenols may have some role in reducing bacterial growth in the oral flora and intestinal biome [37]. Reducing the impact of age related diseases such as AD may depend on enhancing immunological memory through methods such as vaccination and suppressing aberrant innate immune response against self, likely in a manner similar to preventing rejection in tissue transplants. With immunosensescence, immunotolerance may have been lost. Restoring immunotolerance calls for suppression of aberrant innate and adaptive immunity, similarly to the approach taken in treating allografts. Medicaitons such as mycophenolate may be helpful in this regard as well as the calcineurin inhibitors.

Besides calcineurin, chronic overexpression of regulator of calcineurin (RCAN1) as occurs in Down's Syndrome/Trisomy 21, also referred to as Down's Syndrome Critical region 1 (DSCR1) which is encoded on chromosome 21, also occurs in AD. RCAN1 expression is up-regulated in aging, the greatest risk factor for late onset AD, and also by Beta-amyloid [38]. Beta-amyloid is secreted or shed in response to microbial infection in the CNS, likely due to immunosensecence related to aging, possibly from latent CMV, as well as reactivation of latent Herpes viruses. This sequence of events in the elderly recapitulates the events in Trisomy 21, which almost invariably leads to onset of AD at an earlier age than usually presents in late onset AD.

While a negative feedback loop for calcineurin and DSCR1/RCAN1 is present, it is likely overwhelmed in AD and Trisomy 21 [39]. People with the ApoE genotype epsilon4/epsilon4, a high-risk genotype for developing AD have higher levels of RCAN1 in lymphocytes than people with lower risk genotypes. RCAN1 upregulates glycogen synthase, a tau kinase, which would increase tau phosphorylation when RCAN1 is upregulated, hyperphosphorylated tau being characteristic of AD. Beta-amyloid causes such upregulation, so RCAN1 links the two hallmarks of AD, Beta-amyloid in Alzheimer plaques and hyperphosphorylated tau in neurofibrillary tangles [40]. It may be possible to lessen the effects of RCAN1 overexpression through dietary measures.

This has been investigated in an experimental study involving fish oil supplement provided to mice, and there was a modest reduction of RCAN1 RNA and protein following such dietary intervention. It was thought such a dietary intervention for persons with Down's syndrome might have some benefit [41]. In a study involving neuronal cell culture, lycopene reduced adverse effects of RCAN1 through reducing oxidative stress and apoptosis, indicating a diet including lycopene- containing foods could have beneficial effects for persons with Down's syndrome or AD [42]. Considering that calcinerin and RCAN1 regulate calcium and the interrelationship of calcium and vitamin D, vitamin D status likely has involvement in AD risk.

In a study involving vitamin D levels in older adults, deficient vitamin D levels were associated with nearly a three times higher risk of developing AD [43]. In a comparison of AD incidence between the Monongahela Valley of Pennsylvania, USA, and Ballabgarh, India, the incidence was practically three times higher in the Pennsylvania cohort compared to the cohort in India. Being at higher latitude, the Pennsylvania location would have lower sunshine exposure, and so could possibly have a lower vitamin D status than the lower latitude cohort in Ballabgarh, India [44]. Probably in prevention and management of AD, and also Down's syndrome, avoiding calcium overload by maintaining the negative feedback mechanism between RCAN1 and calcineurin

expression and function is a prime consideration. It may be possible to assess whether the relationship between RCAN1 and calcineurin is optimal through metabolic studies of peripheral blood cells, through assessment of RCAN1 expression level. AD being a multifactorial disease, it's unlikely that one approach to management will fit all.

Further investigations involving immunosenescence and its causes will be helpful in understanding if it has a relationship to pathogenesis of AD and the basic causes of aging, which likely involve additional fields such as epigenetics, activity and exercise, susceptibility to infections and the many aspects of calcium metabolism and signaling.

Author Contributions

The author made all contributions to this work.

Competing Interests

The author has declared that no competing interests exist.

References

1. Squitti R, Ghidoni R, Simonelli I, Ivanova ID, Colabufo NA, Zuin M, et al. Copper dyshomeostasis in Wilson disease and Alzheimer's disease as shown by serum and urine copper indicators. J. Trace Elem Med Biol . 2018; 45: 181-188.
2. Ventriglia M, Brewer GJ, Simonelli I, Mariani S, Siotto M, Bucossi S, et al. Zinc in Alzheimer's disease: a meta-analysis of serum, plasma, and cerebrospinal fluid studies. J Alzheimers Dis. 2015; 46: 75-87.
3. Tao Y, Wang Y, Rogers JT, Wang F. Perturbed iron distribution in Alzheimer's disease serum, cerebrospinal fluid, and selected brain regions: a systematic review and meta-analysis. J Alzheimers Dis. 2014; 42: 679-690.
4. Zapatero M, de Jalon AG, Pascual F, Calvo M, Escanero J, Marro A. Serum aluminum levels in Alzheimer's disease and other senile dementias. Biol Trace Elem Res. 1995; 47: 235-240.
5. Sochocka M, Zwolinska K, Leszek J. The infectious etiology of Alzheimer's Disease. Curr Neuropharmacol. 2017; 15: 996-1009.
6. Mayeux R, Stern Y. Epidemiology of Alzheimer disease. Cold Spring Harb Perspect Med. 2012: a006239.
7. Nikolich-Žugich J. Aging of the T cell compartment in mice and humans: from no naive expectations to foggy memories. J Immunol. 2014; 193: 2622-2629.
8. Keswani T, Mitra S, Bhattacharyya A. Copper-induced immunotoxicity involves cell cycle arrest and cell death in the liver. Environ Toxicol. 2015; 30: 411-421.
9. Cunningham-Rundles S, McNeeley DF, Moon A. Mechanisms of nutrient modulation of the immune response. J Allergy Clin Immunol. 2005; 115: 1119-1128.
10. Cherayil BJ. Iron and immunity: immunological consequences of iron deficiency and overload. Arch Immunol Ther Exp. 2010; 58: 407-415.
11. Zhu Y, Hu C, Li X, Shao B, Sun H, Zhao H, et al. Suppressive effects of aluminum trichloride on the T lymphocyte immune function of rats. Food Chem Toxicol. 2012; 50: 532-535.

12. Spencer JV, Lockridge KM, Barry PA, Lin G, Tsang M, Penfold ME, et al. Potent immunosuppressive activities of cytomegalovirus-encoded interleukin-10. J Virol. 2002; 76: 1285-1292.
13. Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, et al. The Alzheimer's disease-associated amyloid β-protein is an antimicrobial peptide. Plos One. 2010; 5: e9505.
14. Fulop T, Witkowski JM, Bourgade K, Khalil A, Zerif E, Larbi A, et al. Can an infection hypothesis explain the beta amyloid hypothesis of Alzheimer's disease? Front Aging Neurosci. 2018; 10.
15. Readhead B, Haure-Mirande J-V, Funk CC, Richards MA, Shannon P, Haroutunian V, et al. Multiscale analysis of independent Alzheimer's cohorts finds disruption of molecular, genetic, and clinical networks by human herpesvirus. Neuron. 2018.
16. Pisa D, Alonso R, Rábano A, Rodal I, Carrasco L. Different brain regions are infected with fungi in Alzheimer's disease. Sci Rep. 2015; 5: 15015.
17. How KY, Song KP, Chan KG. Porphyromonas gingivalis: an overview of periodontopathic pathogen below the gum line. Front. Microbiol. 2016; 7: 53.
18. DeLeon-Pennell KY, de Castro Brás LE, Lindsey ML. Circulating Porphyromonas gingivalis lipopolysaccharide resets cardiac homeostasis in mice through a matrix metalloproteinase-9-dependent mechanism. Physiol Rep. 2013; 1.
19. Lorenzl S, Albers DS, Relkin N, Ngyuen T, Hilgenberg SL, Chirichigno J, et al. Increased plasma levels of matrix metalloproteinase-9 in patients with Alzheimer's disease. Neurchem Int. 2003; 43: 191-196.
20. Khare SD, Dokholyan NV. Molecular mechanisms of polypeptide aggregation in human diseases. Curr Protein Pept Sci. 2007; 8: 573-579.
21. Moir RD, Lathe R, Tanzi RE. The antimicrobial protection hypothesis of Alzheimer's disease. Alzheimers Dement. 2018; 14: 1602-1614.
22. Ren H, Teng Y, Tan B, Zhang X, Jiang W, Liu M, et al. TLR triggered calcium mobilization protects mice against bacterial infection through extracellular ATP release. Infect Immun. 2014: IAI. 02546-02514.
23. Kang YJ, Kusler B, Otsuka M, Hughes M, Suzuki N, Suzuki S, et al. Calcineurin negatively regulates TLR-mediated activation pathways. J Immunol. 2007; 179: 4598-4607.
24. O'Neal MA, Stallings NR, Malter JS. Alzheimer's Disease, Dendritic Spines, and Calcineurin Inhibitors: A New Approach? : ACS Publications; 2018.
25. Rozkalne A, Hyman BT, Spires-Jones TL. Calcineurin inhibition with FK506 ameliorates dendritic spine density deficits in plaque-bearing Alzheimer model mice. Neurobiol Dis. 2011; 41: 650-654.
26. Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science. 2016; 352: 712-716.
27. Hung AY, Koo EH, Haass C, Selkoe DJ. Increased expression of beta-amyloid precursor protein during neuronal differentiation is not accompanied by secretory cleavage. Proc Natl Acad Sci. 1992; 89: 9439-9443.
28. Wang B, Li H, Ozseker SA, Bowser DA, Moore MJ, Wang MC, et al. The amyloid precursor protein is a conserved receptor for slit to mediate axon guidance. eNeuro. 2017: 0185-0117.
29. Reese LC, Zhang W, Dineley KT, Kayed R, Taglialatela G. Selective induction of calcineurin activity and signaling by oligomeric amyloid beta. Aging cell. 2008; 7: 824-835.

30. Blair LJ, Baker JD, Sabbagh JJ, Dickey CA. The emerging role of peptidyl-prolyl isomerase chaperones in tau oligomerization, amyloid processing, and Alzheimer's disease. J Neurochem. 2015; 133: 1-13.
31. Yates SC, Zafar A, Rabai EM, Foxall JB, Nagy S, Morrison KE, et al. The effects of two polymorphisms on p21cip1 function and their association with Alzheimer's disease in a population of European descent. Plos One. 2015; 10: e0114050.
32. Castaneda-Delgado J, Miranda-Castro N, Gonzalez-Amaro R, Gonzalez-Curiel I, Montoya-Rosales A, Rivas-Calderon B, et al. Production of antimicrobial peptides is preserved in aging. Clin Immunol. 2013; 148: 198-205.
33. Tramutola A, Abate G, Lanzillotta C, Triani F, Barone E, Iavarone F, et al. Protein nitration profile of CD3+ lymphocytes from Alzheimer disease patients: Novel hints on immunosenescence and biomarker detection. Free Radic Biol Med. 2018; 129: 430-439.
34. Peiris H, Keating DJ. The neuronal and endocrine roles of RCAN 1 in health and disease. Clin Exp Pharmacol Phsiol. 2018; 45: 377-383.
35. Miklossy J, Qing H, Radenovic A, Kis A, Vileno B, Làszló F, et al. Beta amyloid and hyperphosphorylated tau deposits in the pancreas in type 2 diabetes. Neurobiol Aging. 2010; 31: 1503-1515.
36. Lefèvre-Arbogast S, Gaudout D, Bensalem J, Letenneur L, Dartigues J-F, Hejblum BP, et al. Pattern of polyphenol intake and the long-term risk of dementia in older persons. Neurology. 2018: 10; 1212.
37. Brenner SR. Reader Response: Polyphenols in the diet may inhibit development of Alzheimer disease by antibiotic effects on bacteria in the intestinal biome and oral flora. Neurology 2018.
38. Cook CN, Hejna MJ, Magnuson DJ, Lee JM. Expression of calcipressin1, an inhibitor of the phosphatase calcineurin, is altered with aging and Alzheimer's disease. J Alzheimers Dis. 2005; 8: 63-73.
39. Sun X, Wu Y, Herculano B, Song W. RCAN1 overexpression exacerbates calcium overloading-induced neuronal apoptosis. Plos One. 2014; 9: e95471.
40. Lloret A, Badia M-C, Giraldo E, Ermak G, Alonso M-D, Pallardó FV, et al. Amyloid-β toxicity and tau hyperphosphorylation are linked via RCAN1 in Alzheimer's disease. J Alzheimers Dis. 2011; 27: 701-709.
41. Zmijewski PA, Gao LY, Saxena AR, Chavannes NK, Hushmendy SF, Bhoiwala DL, et al. Fish oil improves gene targets of Down syndrome in C57BL and BALB/c mice. Nutr Res. 2015; 35: 440-448.
42. Lim S, Hwang S, Yu JH, Lim JW, Kim H. Lycopene inhibits regulator of calcineurin 1-mediated apoptosis by reducing oxidative stress and down-regulating Nucling in neuronal cells. Mol Nutr Food Res. 2017; 61: 1600530.
43. Feart C, Helmer C, Merle B, Herrmann FR, Annweiler C, Dartigues J-F, et al. Associations of lower vitamin D concentrations with cognitive decline and long-term risk of dementia and Alzheimer's disease in older adults. Alzheimers Dement. 2017; 13: 1207-1216.
44. Chandra V, Pandav R, Dodge H, Johnston J, Belle S, DeKosky S, et al. Incidence of Alzheimer's disease in a rural community in India: the Indo–US study. Neurology. 2001; 57: 985-989.

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