Reconsideration of Alzheimer’s Disease Therapy from a Viewpoint of Amyloidogenic Evolvability

Gilbert Ho¹, Pei Chen Choo¹, Masaaki Waraga², Satoshi Inoue³,⁴, Eliezer Masliah⁵ and Makoto Hashimoto²,∗

¹PCND Neuroscience Research Institute, Poway, CA, USA
²Tokyo Metropolitan Institute of Medical Science, Setagaya-ku, Tokyo, Japan
³Department of Systems Aging Science and Medicine, Tokyo Metropolitan Institute of Gerontology, Itabashi-ku, Tokyo, Japan
⁴Research Center for Genomic Medicine, Saitama Medical University, Saitama, Japan
⁵Division of Neuroscience, National Institute on Aging, Bethesda, MD, USA

Received 8 April 2021
Accepted 3 April 2022
Pre-press 22 April 2022
Published 27 April 2022

Abstract. Presuming that Alzheimer’s disease (AD) might represent an antagonistic pleiotropic phenomenon derived from the evolvability of multiple amyloidogenic proteins, targeting such proteins simultaneously could enhance therapeutic efficacy. Furthermore, considering that amyloid-β (Aβ) immunotherapies during reproductive life stage might adversely decrease Aβ evolvability in an offspring’s brain, the disease-modifying Aβ immunotherapies should be limited to post-reproductive time in lifespan. Thus, current Aβ immunotherapy strategies should be revised accordingly. Given that the “adiponectin paradox” might underlie both amyloidosis and cognitive dysfunction in aging brain, blocking activin signaling situated downstream of the adiponectin paradox might be an alternative strategy to prevent AD.

Keywords: Activin, adiponectin paradox, Alzheimer’s disease (AD), amyloid-β immunotherapy, antagonistic pleiotropy, evolvability, follistatin

Despite two decades of Alzheimer’s disease (AD) clinical therapeutics, the prevailing strategy of amyloid-β (Aβ) immunotherapy has never convincingly met all benchmarks for therapeutic efficacy. Furthermore, early Aβ immunotherapy trials employing active recombinant Aβ32 immunization were suspended due to encephalomyelitis [1]. Notably, a dissociation has existed where histologically demonstrated improvement in Aβ neuropathology in AD patients, was paired with a lack of improvement in clinical dementia [2, 3]. Newer passive Aβ immunotherapies in aged patients using monoclonal and polyclonal Aβ antibodies [4] have also shown little clinical benefit (Fig. 1A).

The precise reasons for Aβ immunotherapy failure in AD remain elusive. Central to this remains our incomplete understanding of the normal physiology of amyloidogenic proteins (APs), like Aβ and tau, relevant to neurodegenerative disease. Consequently, we proposed evolvability as a novel physiological function of APs in neurodegeneration [5, 6]. Specifically, as APs consist of intrinsically disor-
Evolvability in offspring and AD in parental aging are driven by aggregation of APs, and these states are proposed to exist in an antagonistic pleiotropy relationship. A) Conventional active Aβ immunotherapies carried out for AD during aging have proved unsatisfactory and unforeseen side effects. B) Second generation disease-modifying Aβ immunotherapies potently inhibit various stages of Aβ aggregation, resulting in both suppression of Aβ evolvability and AD. Thus, disease-modifying Aβ immunotherapy is beneficial to the older AD patients, but detrimental to their offspring. C) The adiponectin paradox-activin signaling pathway is involved in the regulation of Aβ evolvability, and later during aging, in which activin may promote AD neurodegeneration through the antagonistic pleiotropy mechanism. Therefore, treatment with the activin-binding molecule, follistatin, or analogues [25, 26], may be effective in preventing activin-induced AD neurodegeneration.

Fig. 1. Diagram illustrating the various effects of therapeutic strategies on amyloidogenic evolvability and neurodegenerative disorders. Evolvability in offspring and AD in parental aging are driven by aggregation of APs, and these states are proposed to exist in an antagonistic pleiotropy relationship. A) Conventional active Aβ immunotherapies carried out for AD during aging have proved unsatisfactory and unforeseen side effects. B) Second generation disease-modifying Aβ immunotherapies potently inhibit various stages of Aβ aggregation, resulting in both suppression of Aβ evolvability and AD. Thus, disease-modifying Aβ immunotherapy is beneficial to the older AD patients, but detrimental to their offspring. C) The adiponectin paradox-activin signaling pathway is involved in the regulation of Aβ evolvability, and later during aging, in which activin may promote AD neurodegeneration through the antagonistic pleiotropy mechanism. Therefore, treatment with the activin-binding molecule, follistatin, or analogues [25, 26], may be effective in preventing activin-induced AD neurodegeneration.

dered structures [7] corresponding to diverse brain stressors, their protofibrils might transmit stress information to offspring via germ cells in a prion-like fashion [8]. Supposing that amyloidogenic evolvability might critically influence the success of amyloid immunotherapy, our objective is to re-imagine amyloid immunotherapy from this unique standpoint.

Much remains unknown about the precise nature of AD pathogenesis and the role of amyloid immunotherapy. In our opinion, two key issues should be addressed. First, it must be determined whether Aβ remains the critical pathogenic and therapeutic target in AD. Certainly, all recent Aβ immunotherapy AD trials are based on the amyloid cascade hypothesis which places Aβ centrally in AD pathogenesis [9]. Yet, because of failed Aβ immunotherapy casting doubt on traditional hypotheses, interest has shifted toward tau as the next therapeutic target [10]. Beyond Aβ and tau, however, other novel APs might also interact with and be critical to AD pathogenesis. Targeting these may turn out to be essential for linking reduced AD pathology to a clinically meaningful therapeutic outcome. In this regard, our view of amyloidogenic evolvability suggests that a number of APs might be involved in evolvability against multiple brain stressors, and that neurodegenerative disease might be a result of antagonistic pleiotropy derived from amyloidogenic evolvability [8]. In addition to Aβ and tau, several other APs have been characterized in AD brain, including p53 [11], amylin [12], and adrenomedullin [13], suggesting that immunotherapy against a singular AP might be insufficient to generate a clinical benefit.

Second, although the design of amyloid immunotherapy trials has been successively optimized over time, challenges remain. Initially, since the timing of treatment in previous Aβ immunotherapy occurred too late in the disease course to exert any benefits for the neurodegenerative process, later passive Aβ immunotherapies have been staged progressively earlier into mild cognitive impairment and eventually into asymptomatic stages such as in the dominantly
inherited AD cohort [14]. While two monoclonal antibodies failed to improve cognition in phase II/III trials, one monoclonal antibody, aducanumab, co-developed by Eisai and Biogen, was controversially approved by the US Food and Drug Administration with a restricted use [15]. However, according to our evolvability hypothesis, one may be concerned that increasingly earlier initiation of disease-modifying therapy for AD treatment/prevention may extend into younger reproductive life, negatively affecting amyloidogenic evolvability (Fig. 1B).

Yet, given that amyloid immunotherapy during younger reproductive life might suppress protofibril formation of APs, leading to reduced amyloidogenic evolvability, this could adversely increase susceptibility to stressors in offspring, causing various pathologies. For instance, it is probable that psychiatric disease including schizophrenia might manifest in offspring due to the decreased Aβ evolvability [16]. Furthermore, neuropathic types of lysosomal storage disorders, such as Niemann-Pick disease and Gaucher disease, might be attributed to decreased AP evolvability, involving Aβ and α-synuclein [17]. Notwithstanding the importance of a possible trans-generational effect of amyloid immunotherapy on offspring/youth, no studies have yet addressed this question. This should not only be assessed using in vivo models, but also more importantly in follow up assessments of patients already treated with amyloid immunotherapies and especially their offspring.

In conclusion, taking into account the physiological properties of APs, including potentially antagonistic pleiotropy and relevant interactions, will be critical when designing any AD therapy strategy, and mechanisms that address multiple APs such as activin signaling, might prove therapeutically significant.

ACKNOWLEDGMENTS

We are grateful for the continuous encouragement of Drs. Kaori Hashimoto (Tokyo Metropolitan Institute of Medical Science) and Maria del Carmen Ruiz de la Cruz (University of Chicago).

FUNDING

The authors have no funding to report.

CONFLICTS OF INTEREST

Gilbert Ho declares that he has previously served on an advisory board for Biogen. The remaining authors declare no conflicts of interest.

REFERENCES

[1] Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, Jouanny P, Dubois B, Eisner L, Flitman S, Michel BF, Boada M, Frank A, Hock C (2003) Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. Neurology 61, 46-54.

[2] Serrano-Pozo A, Christopher A, William M, Ferrer I, Uro-Coste E, Delisie MB, Maurage CA, Hock C, Nitsch RM,
Bateman RJ, Aschenbrenner, AJ, Benzinger TLS, Clifford Fernandez AP, Masa JS, Guedan MA, Futch HS, Jackson K, Gustavo A, Barisone GA, Diaz E, Jin LW, Congdon EE, Sigurdsson EM (2018) Tau-targeting therapy for Alzheimer’s disease: Is it now a long shot? *Ann Neurol* **85**, 303-315.

Hashimoto M, Ho G, Sugama S, Takamatsu Y, Shimizu Y, Takenouchi T, Waragai M, Masliah E (2018) Evolvability of amyloidogenic proteins in human brain. *J Alzheimer’s Dis* **62**, 73-85.

Kirschner M, Gerhart J (1998) Evolvability. *Proc Natl Acad Sci USA* **95**, 8420-8427.

Uversky VN (2017) Intrinsically disordered proteins in overcrowded milieu: Membrane-less organelles, phase separation, and intrinsic disorder. *Curr Opin Struct Biol* **44**, 18-30.

Hashimoto M, Ho G, Takamatsu Y, Shimizu Y, Sugama S, Takenouchi T, Waragai M, Masliah E (2018) Evolvability and neurodegenerative disease: Antagonistic pleiotropy phenomena derived from amyloid aggregates. *J Parkinson’s Dis* **8**, 405-408.

Selkoe DJ and Hardy J (2016) The amyloid hypothesis of Alzheimer’s disease at 25 years. *EMBO Mol Med* **8**, 595-608.

Congdon EE, Sigurdsson EM (2018) Tau-targeting therapies for Alzheimer disease. *Nat Rev Neurol* **14**, 399-415.

Szyblik A, Lesniak W (2017) P53 Dysfunction in neurodegenerative diseases - the cause or effect of pathological changes? *Aging Dis* **8**, 506-518.

Jackson K, Gustavo A, Barisone GA, Diaz E, Jin LW, DeCarli C, Despa F (2013) Amylin deposition in the brain: A second amyloid in Alzheimer disease? *Ann Neurol* **74**, 517-526.

Fernandez AP, Masa QA, Guedan MA, Futch HS, Martinez-Murillo R (2016) Adrenomedullin expression in Alzheimer’s brain. *Curr Alzheimer Res* **13**, 428-438.

Bateman RJ, Aschenbrenner, AJ, Benzenziger TLS, Clifford D, Kelley Coarer K, Cruchaga C, Fagan AM, Farlow MR, Goate AM, Gordon BA, Hassenstahl J, Jack Jr. CR, Koepp RA, McDeade E, Mills S, Morris JC, Sallaway SP, Santacruz A, Snyder PJ, Wang G, Xiong C, Snider BJ, Mummery RA, Murrey CJ, Surti GM, Hannequin D, Wallon D, Berman S, Lah A, Snyder PJ, Wang G, Xiong C, Honig CJ, Sanchez-Valle R, Brooks WS, Gauthier S, Masters CL, Galasko DR, Brosch JR, Hsiaung GYR, Jayadev S, Formaglio M, Masellis M, Clarinette R, Pariente J, Dubois B, Pasquier F, Andersen SW, Holdridge KC, Mintun MA, Sims JR, Yaari R, Badler M, Delmar P, Doody R, Fontoura P, Kerchner GA, DIAN-TU Study (2020) Overview of dominantly inherited AD and top-line DIAN-TU results of solanezumab and gantenerumab: Results of the DIAN-TU prevention trial of solanezumab and gantenerumab in dominantly inherited AD. *Alzheimers Dement* **16**, e041129.

U.S. Food and Drug Administration (2021) FDA Grants Accelerated Approval for Alzheimer’s Drug. Silver Spring, MD https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug

Takamatsu Y, Ho G, Waragai M, Sugama S, Wada, R, Sugama S, Takenouchi T, Masliah E, Hashimoto M (2019) Transgenerational interaction of Alzheimer’s disease with schizophrenia through amyloid evolvability. *J Alzheimer’s Dis* **68**, 473-481.

Wei J, Takamatsu Y, Wada, R, Fujita M, Ho G, Takenouchi T, Masliah E, Hashimoto M (2021) Therapeutic potential of αS evolvability for neuropsychiatric Gaucher disease. *Biomolecules* **11**, 289.

Namwanje M, Brown CW (2016) Activins and inhibins: Roles in development, physiology, and disease. *Cold Spring Harbor Perspect Biol* **8**, a021881.

Town T, Laourer Y, Pittenger C, More T, Szekely CA, Tan J, Duman RS, Flavell RA (2008) Blocking TGF-beta-Smad2/3 innate immune signaling mitigates Alzheimer-like pathology. *Nat Med* **14**, 681-687.

Sente T, Van Berendoncks AM, Hoymans VH, Vrints CJ (2016) Adiponectin resistance in skeletal muscle: Pathophysiological implications in chronic heart failure. *J Cachexia Sarcopenia Muscle* **7**, 261-274.

Waragai M, Ho G, Takamatsu Y, Wada R, Sugama S, Takenouchi T, Masliah E, Hashimoto M (2020) Adiponectin paradox in Alzheimer’s disease: relevance to amyloidogenic evolvability? *Front Endocrinol (Lausanne)* **11**, 108.

Waragai M, Ho G, Takamatsu Y, Wada R, Sugama S, Takenouchi T, Masliah E, Hashimoto M (2020) Adiponectin paradox as a therapeutic target in Alzheimer’s disease. *J Alzheimer’s Dis* **76**, 1249-1253.

Hashimoto M, Ho G, Sugama S, Takenouchi T, Waragai M, Sugino H, Inoue S, Masliah E, (2021) Possible role of activin in the adiponectin paradox-induced progress of Alzheimer’s disease *J Alzheimer’s Dis* **81**, 451-458.

Nakamura T, Takio K, Eto Y, Shibai H, Titani, K, Sugino H (1999) Activin-binding protein from rat ovary is follistatin. *Science* **247**, 836-838.

Shen C, Iskenderian A, Lundberg D, He T, Palmieri K, Crooker R, Deng Q, Taylor M, Gu S, Haojing Rong H, Ehmann D, Pescatore B, Strack-Logue B, Romashko A, Baviello G, Gill J, Zhang B, Meiyappan M, Clark Pan C, Norton AW (2018) Protein engineering on human recombinant follistatin: Enhancing pharmacokinetic characteristics for therapeutic application. *J Pharmacol Exp Ther* **366**, 291-302.

Tsuchida K (2008) Myostatin inhibition by a follistatin-derived peptide ameliorates the pathophysiology of muscular dystrophy model mice. *Acta Myol* **27**, 14-18.