

Is Alzheimer an Autoimmune Disease Gone Rogue?

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ABSTRACT

It is posited that the compromised integrity of the blood brain barrier is a component of the etiology of Alzheimer disease, not a consequence of it. It is further submitted that the root cause of the disease is the brain's autoimmune system having gone rogue in its unsuccessful attempts at maintaining brain homeostasis. Previous attempts at managing the disease risks are only palliative and do not address the root cause of the disease. In analogy with cancer and type-1 diabetes treatments, it is proposed to employ immunotherapy (natural or synthetic with chimeric antigen T(reg) or PD-1 cells) with the purpose of regulating the brain autoimmune system (not to either fiercely combating it or suppressing it totally). There may be additional possible therapeutic approaches, but one should always be cautious about triggering other autoimmune diseases.

Key words: Alzheimer disease; blood brain barrier; brain homeostasis; autoimmune system regulation.

INTRODUCTION

There are approximately 400 known neurological diseases, some of which classified as mental disorders. A number of these disorders are mediated by a disruption or failure of the blood-brain barrier. Unfortunately, the convergence between the barrier studies and clinical investigations has historically been limited. Nonetheless, in the case of Alzheimer, I will posit that the compromised integrity of the barrier is a component of the etiology of the disease, not a consequence of it.^[1-3] I will further submit that the root cause of the disease is the brain's autoimmune system having gone rogue (a sort of "run away" effect) in its unsuccessful attempts to maintain brain homeostasis between the antagonistic synaptoblastic and synaptoclastic pressures. The cure, as discussed later, would be to balance these pressures by regulating the system rather than fiercely combating either the hyper-excited synaptoblastic pressures or/and suppressing the synaptoclastic ones.

Over the past few decades, Alzheimer disease, once considered a rare disorder, has emerged from obscurity to become a major public health problem. Based on a lack of

treatment, it has been generally considered as an irreversible, progressive brain disease that slowly destroys memory and thinking skills, eventually even the ability to carry out the simplest tasks. It is a chronic neurodegenerative disorder of poorly (or not) understood cause(s). Based on identified risk factors, several theories (hypotheses) have been propounded for its cause(s) beyond genetics (early onset familial disease, late-onset sporadic disease): Cholinergic, amyloid, fungal infection, tau, neurovascular, neuroinflammation, neurodevelopmental, cardiovascular, gum disease infection, dysfunction of oligodendrocytes, and others related to lifestyle, diet, and the environment.^[4-8] Such a wide array of hypotheses is by itself indicative of our lack of true understanding and knowledge of the disease notwithstanding the fact that the disease has been identified since 1901 and has been the subject of a considerable number of publications dealing with it (in excess of 50,000, according to some authors).

Despite claims by some research clinicians,^[4-7] there are currently no known treatments if only to stop or reverse the progression of the disease. Some of these alleged "treatments," including the advocated program ("DESS:" Diet, exercise, stress, sleep, and variations on this theme) are

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palliative in nature, temporarily improving symptoms, while the disease progresses unabated. One must keep in mind that risk is not causation and risk management is not treatment! Research has rather focused on diagnosing the condition before symptoms begin. Thus, a number of biochemical tests have been developed to attempt earlier detection including analysis of the cerebrospinal fluid for beta-amyloid (A β) or tau proteins and preventive anti-body vaccination. Neuroprotective agents (e.g., AI-108, PBT2, and TNF α receptor-blocking fusion protein etanercept) have also been designed. Further, among the more than 400 pharmaceutical treatments having been investigated or in advanced clinical trials, putative pharmaceutical therapies attempt to treat the underlying disease pathology such as by reduction of A β levels (e.g., by apomorphine, investigational immunotherapy, or vaccination) and inhibiting tau aggregation (e.g., with methylthioninium chloride and dimebon). Again, however helpful, such tests are not curative. Still, other “softer” methodologies involve meditation and antifungal infection of the brain.

Putative immunological therapies, based on the concept of training the immune system to recognize, attack, and reverse the deposition of A β have been designed. Unfortunately, such a surrogate end-point has not been clinically demonstrated to cure the disease, i.e., even after the amyloid plaques had been removed, the disease symptoms persisted, and the disease itself continued its deleterious progress. In addition, immunotherapeutic agents have been found to cause some concerning adverse drug reactions. Still further, one important limitation of active and passive immunotherapy as currently practiced is the low amount of antibodies that can pass the blood-brain barrier (this may, however, be overcome by coupling antibodies to the peptide penetration). In distinction with the antibodies employed, several small molecules have been designed to readily pass the barrier while delivering therapeutic compounds at the right locations in the right dosage amounts, heralding a new treatment approach. This is also what nanomedicine and nanotechnology promise to do. However, while the technology is now well known, its application to neurodegenerative disorders has not yet been undertaken.

In brief, while palliative treatments are available, neurodegenerative disorders in general, and Alzheimer, in particular, have generally been declared as incurable. The reason is that we have not yet been able to identify the etiology and deep biology of their root cause(s). This situation is reminiscent of that for other diseases, particularly cancer. It was not until after we came to the realization that cancerous cells like healthy cells from which they evolve are braided in our genome, and that cancer is not an organ disease but the result of multiple genetic mutations, i.e., understanding the deep biology of cancer, that we have made great strides in cancer treatment and cure. Witness the emergence of

immuno-oncology and the recent FDA-approved use of chimeric antigen receptor (CAR) T-cells.^[9-11] Immunotherapy has been successful in inducing long-term remissions of hard-to-treat cancers. The early identified protein receptor on the surface of T-cells (cytotoxic T-lymphocyte antigen 4, [CTL-4]) and a molecule (programmed death 1, PD-1) led to astonishing tumor shrinkage and increased survival, particularly in metastatic melanoma. Thus, anti-CTL-4 and anti-PD-1 have opened up new vistas in tumor treatment. Beyond that, genetically modified patients' T-cells and PD-1 molecules promise to be even more effective in specifically tailoring the treatment to the patient along the precepts of personalized medicine.

To employ immunotherapy in the case of Alzheimer implies that the brain has immune capabilities. In the past, due to the presence of the brain's protective barriers at the interface between the central nervous system and the periphery, and their muted response to neuroinflammation, it had been widely assumed heretofore that the brain (and, more generally, the central nervous system) is immune-privileged. However, in contrast to this earlier dogma, it is now evident that these immune capabilities exist. The brain's vaguely understood component of the immune system is normally able to handle, treat, and overcome any adverse pathologies developing therein. It fails when the insult is so unsurmountable as to cause the immune system to go haywire. Despite the protective mechanisms of the barriers, the capacity for immune-surveillance of the brain is maintained, and there is evidence of inflammatory signaling at the brain barriers that may be an important part of the body's response to damage or infection. This signaling system appears to change both with normal aging and during disease. Changes may affect organic phenomena (or diapedesis) of immune cells and active molecular transfer or cause rearrangement of the tight junctions and an increase in passive permeability across barrier interfaces. In parallel with immunotherapy as an emergent therapy of cancer, I advanced earlier the opinion that brain immunotherapy should also become a similar therapy for brain cancers and neurological disorders, providing a paradigm shift in our therapeutic approach to brain cancer and these disorders.^[9-14]

I now posit that the root cause of Alzheimer is the brain's very autoimmune system that had run amok in its attempts to maintain brain homeostasis. This balancing process consists of two phases: (a) The synapse - building or “synaptoblastic” phase: Neurons sport receptors called amyloid precursor proteins that grab hold of netrin-1 (molecules floating by in the intercellular environment) and send signals to the neurons to keep them healthy and functional; and when this process fails (b) the synapse -destroying or “synaptoclastic” phase: It defaults to opposite signals that instruct the neurons to commit

suicide and to the amyloid precursor proteins to produce more A β thereby outnumbering netrin-1. As a consequence, the amyloid precursor proteins are less likely to grab netrin-1 and more likely to keep grabbing A β . Any effective treatment for Alzheimer should, therefore, include a method to rebalance the synapse building and dismantling phases, not enhancing or destroying either phase.^[4,5,12-16]

The approach advocated here would be to regulate the underlying autoimmune system (not to either enhance it immeasurably or suppress it totally), to boost in a measured manner the synaptoblastic signals while at the same time taming down the synaptoclastic signals. This idea builds on work done in diabetes type I, an incurable disease so far, in which the autoimmune system is taught to tolerate the insulin-producing cells of the pancreas so that it does not destroy the diabetic patient's ability to produce the glucose-regulating insulin.^[17,18] The similar idea forms the basis of various clinical trials for treating other incurable diseases such as multiple sclerosis and Graves's disease. The overarching purpose is to tame down the hyperactive autoimmune system by employing molecules that can induce an immune response (antigens) or engineered immune cells that can train the autoimmune system to tolerate the process or tissue it is on track to damage. This idea has the potential to cure a range of autoimmune disorders, including especially neurological and neurodegenerative disorders and especially Alzheimer. As stated earlier in the case of cancer and brain tumors, this requires a deep understanding of the molecular basis of autoimmunity, including brain and central nervous system immunity, as well as advances in genetic engineering and cell-based therapy. Caution must nonetheless be exercised as deploying the immune system to treat certain diseases can also potentially trigger other autoimmune diseases, for example, in the case of cancer, it may additionally trigger rheumatoid arthritis and colitis.

The main immune players are the regulatory T-cells (T_{reg}), which act as the brakes of the immune system. Similarly to other T-cells, T_{reg}-cells rein in the immune cells that are doing damage. It has been suggested that the body can be made to produce the T_{reg}-cells required to dampen a certain autoimmune response, by dosing people who are affected with the same antigen or antigens that the immune system wrongly interprets as a reason to attack. This was tested^[17,18] for multiple sclerosis, demonstrating less brain inflammation. The approach is similar to vaccination without the immune-system stimulants called adjuvants that are usually included in vaccine formulations. Here, antigens can induce a calming effect through T_{reg}-cells.

There may be other ways to temper a rogue autoimmune system. For example, in cell-based therapy, a patient's T_{reg}-cells can be removed from the body, engineered to respond to

specific antigens that have been wrongly recognized by the immune system as being foreign, and then returned. This is the very principle of FDA-approved CAR T-cells (here T_{reg}-cells) that have been applied to cancer treatment.^[12,13] They can also be used to dampen harmful inflammation.

CONCLUSION

A number of known neurological and neurodegenerative disorders are mediated by a disruption or failure of the blood-brain barrier. While understanding the nature of the barrier's role (and also the role of multidrug resistance) is imperative in designing treatments, the fundamental question of whether the compromised integrity of the barrier is a component of the etiology of the disease under consideration or a consequence of it remains unanswered. I have advocated for the former instance. Like in other diseases (diabetes, cancer, etc.), we have been hampered by our imperfect understanding of the underlying biology and, in desperation, have too soon declared such diseases as "incurable." However, the realization that the brain and the central nervous system are endowed with their own immune system, accompanied by the greater understanding of the mechanism of autoimmunity, and the advent of cell-based therapy will empower us to conceive other treatment strategies and even cures as I have attempted to do here in the case of Alzheimer. The main immune players, the regulatory T-cells (T_{reg}), which act as the brakes of the immune system, can be so manipulated (engineered) as to temper and regulate the autoimmune system and train it to tolerate (rather than fiercely combat) the opposing pressures to achieve brain homeostasis. There may also be additional ways to temper a rogue autoimmune system such as emulating cancer immunotherapy with CAR-T cells but with CAR-T_{reg} cells for the neurodegenerative diseases of interest.

REFERENCES

1. Fymat AL. Neurological disorders and the blood brain barrier: 1. Epilepsy. *J Curr Opin Neurol Sci* 2017;1:277-93.
2. Fymat AL. Neurological disorders and the blood brain barrier: 2. Parkinson and other movement disorders. *J Curr Opin Neurol Sci* 2018;2:362-83.
3. Fymat AL. Permeability of the blood brain barrier and neurological diseases. *J Curr Opin Neurol Sci* 2018;2:411-4.
4. Bredesen DE. Reversal of cognitive decline: A novel therapeutic program. *Aging (Albany NY)* 2014;6:707-17.
5. Bredesen DE, Amos EC, Canick J, Ackerley M, Raji C, Fiala M, *et al.* Reversal of cognitive decline in alzheimer's disease. *Aging (Albany NY)* 2016;8:1250-8.
6. Bredesen DE. *The End of Alzheimer: The First Programme to Prevent and Reverse the Cognitive Decline of Dementia.* London: Vermilion; 2017. p. 308.
7. Sherzai D, Sherzai A. *The Alzheimer's Solution: A Breakthrough Program to Prevent and Reverse the Symptoms of Cognitive Decline at Every Age.* New York, NY: Harper Collins; 2018.

- p. 308.
8. Berger A. The Alzheimer's Antidote: Using a Low-Carb, High-Fat Diet to Fight Alzheimer Disease, Memory Loss, and Cognitive Decline. Amy Berger: Chelsea Green Publishing; 2017.
 9. Fymat AL. Immunotherapy of brain cancers and neurological disorders. *J Cancer Prev Curr Res* 2017;8:1-7.
 10. Fymat AL. Immunotherapy: An emergent anti-cancer strategy. *J Cancer Prev Curr Res* 2017;7:1-4.
 11. Fymat AL. Immunotherapy: A new frontier in cancer care. *Holist Approaches Oncother J* 2017;1:8-13.
 12. Fymat AL. Cancer therapy with chimeric antigen receptors-a landmark moment for cancer immunotherapy. *J Cancer Prev Curr Res* 2017;8:1-7.
 13. Fymat AL. Synthetic immunotherapy with chimeric antigen receptors. *J Cancer Prev Curr Res* 2017;7:1-3.
 14. Wraith DC. The future of immunotherapy: A 20-year perspective. *Front Immunol* 2017;8:1668.
 15. Fymat AL. Alzheimer's disease: A review. *J Curr Opin Neurol Sci* 2018;2:415-36.
 16. Fymat AL. Alzheimer's disease: Prevention, delay, minimization and reversal. *J Res Neurol* 2018;1:1-16.
 17. Takiishi T, Gysemans C, Bouillon R, Mathieu C. Vitamin D and diabetes. *Endocrinol Metab Clin North Am* 2010;39:419-46, table of contents.
 18. Alhadj Ali M, Liu YF, Arif S, Tatovic D, Shariff H, Gibson VB, *et al.* Metabolic and immune effects of immunotherapy with proinsulin peptide in human new-onset type 1 diabetes. *Sci Transl Med* 2017;9: pii: eaaf7779.

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