Is Alzheimer's a Runaway Autoimmune Disease? The role of Brain Immunotherapy

Alain L Fymat

International Institute of Medicine & Science, USA

Abstract

Over the past few decades, Alzheimer's 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: cholinergic, amyloidal-beta, tau, viral or fungal infection, neurovascular, neuroinflammation, neurodevelopmental, cardiovascular, gum disease infection, dysfunction of oligodendrocytes, others related to lifestyle, diet, and the environment, and many others. 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 it has been identified and described since 1901, and been the subject of a considerable number of publications dealing with it (in excess of 50,000, according to some authors). Further, one must keep in mind that risk is not causation and risk management is not treatment, only palliation!

Despite claims by some research clinicians, 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 palliative in nature, temporarily improving symptoms... while the disease progresses unabated. 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 amyloidal-beta (Aβ) or tau proteins and preventive anti-body vaccination. Neuroprotective agents (such as, for examples, AI-108, PBT2 and TNFα receptor-blocking fusion protein etarnacept) 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 Aβ levels (e.g., by apomorphine, investigational immunotherapy, or vaccination) and inhibiting tau aggregation (e.g., with methylthionium chloride and dimebon). Again, however helpful, such treatments are not curative. Still other –softer methodologies involve meditation and anti-fungal infection of the brain. In brief, while palliative treatments are available, neurodegenerative disorders in general, and alzheimer's 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).In this article, I posit that the root cause is the brain's autoimmune system having gone rogue in its unsuccessful attempts to maintain brain homeostasis between the antagonistic synaptoblastic and synaptoclastic pressures. The cure would then logically 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.

Putative immunological therapies, based on the concept of training the immune system to recognize, attack, and reverse the deposition of Aβ have been designed. Unfortunately, such a surrogate end-point1 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. Additionally, 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 penetratin). By contrast, and 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, including Alzheimer's, has not yet been undertaken. 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 U.S. FDA-approved use of chimeric antigen receptor (CAR) T-cells. 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 Tlymphocyte 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 patient's T-cells and PD-1 molecules promise to be even more effective in personalized medicine.

To employ immunotherapy in the case of Alzheimer's implies that the brain has immune capabilities. In the past, owing 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 do exist. The brains vaguely understood component of the immune system is normally able to handle, treat, and overcome any adverse pathologies developing therein. It fails when the insults are 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 signalling at the brain barriers

that may be an important part of the body's response to damage or infection. This signalling system appears to change both with normal aging and during rearrangement of the barrier's 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. Having posited that the root cause of Alzheimer's is the brain's very autoimmune system that had run amok in its attempts to maintain brain homeostasis, I must now describe the needed balancing process. It would consist of two phases. In the first phase, 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. When the above process fails, the second phase, the "synapse-destroying" or 2–synaptoclastic phase defaults to opposite signals that instruct the neurons to commit suicide and to the amyloid precursor proteins to produce more Aβ thereby outnumbering netrin-1. As a consequence, the amyloid precursor proteins are less likely to grab netrin-1 and more likely to keep grabbing Aβ. Any effective treatment for Alzheimer's should therefore include a method to rebalance these two phases, synapse-building and synapse-dismantling, not enhancing or destroying either phase.

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. The above idea of balancing two opposing forces builds upon 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. The similar idea also forms the basis of various clinical trials for treating other incurable diseases such as multiple sclerosis and Graves' 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 the potential to cure a range of autoimmune disorders, including especially neurological and neurodegenerative disorders and particularly Alzheimer's. All these instances require 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, e.g., in the case of cancer, it may additionally trigger rheumatoid arthritis and colitis.

The main immune players are the regulatory T-cells (Treg), which act as the brakes of the immune system. Similarly to other T-cells, Treg-cells rein in the immune cells that are doing damage. It has been suggested that the body can be made to produce the Treg-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 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 Treg-cells. There may be other ways to temper a rogue autoimmune system. For example, in

cell-based therapy, a patient's Treg-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 the FDA-approved chimeric antigen receptor (CAR) T-cells (here Treg-cells) that have been applied to cancer treatment. They can also be used to dampen harmful inflammation.

In conclusion, like for 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 (the regulatory T-cells, Treg), 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's.