Alzheimer's Disease and the Immune System

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Abstract

Alzheimer's disease (AD) has been known for over 100 years, but has only just become a pressing matter at the end of the 21st century. AD is a disease related to the aging of the individual, and has its burden over the population has continued to increase as medicine and technology are continuing to lengthen the lives of individuals. Changes in the body associated with aging, such as a weaker immune system, are causing the buildup of the protein associated with AD, amyloid beta (A β). Although the monomer forms of this peptide are a normal occurrence within the body, the oligomer or higher multi-unit forms of the peptide present problems to the neurons and local environment in the CNS. The molecules become toxic to the area, and they are flagged by the body to be cleared. Antibody production, opsonization, and phagocytosis by astrocytes and microglia cells in the brain have been shown to help clear this burden. However, this clearing process also can trigger pro-inflammatory pathways and secrete inflammatory cytokines, and this inflammatory response goes on to further promote the pathological changes associated with AD. One of the major progressors of AD is the dysfunction of the immune system caused by abnormal peptide folding in the CNS. Although the immune system of aged patients tend to be fragile with respect to function, acting through immune modulation and immunotherapy are currently seen to be some of the most beneficial techniques for age related diseases. In this review, we will discuss the relation of AD to age and the immune system, and then introduce the current options and treatments regarding immune modulation and immunotherapy.

Keywords: Alzheimer's disease; Neuroimmunology; Immune modulation; Immune therapy; Beta amyloid; Immunotherapy

Introduction

Aging and inflammation are a couple of the greatest factors and contributors to disease. When examining the top ten causes of disease-related death in the United States, a handful of those are progressed through low levels of chronic inflammation in the senior patients.

Inflammation is a factor in heart disease, stroke, cancer, respiratory disease, diabetes and Alzheimer's disease (AD) [1-6]. This level of chronic inflammation may be a result of cellular or mitochondrial dysfunction [7]. As the levels of inflammation,

both acute and chronic, increase with the level of free radical production in the cell, which may in turn affect the function of the mitochondria. These effects of aging in turn increase inflammation in the body, which may also affect the progression of a person's disease state.

AD is a plight upon the elderly which trickles down to burden the rest of society. It is quickly becoming one of the most economically taxing diseases to developed countries [8,9]. It currently stands as the 6th deadliest of diseases facing the US, and is continuing to rise without any substantial advances in treatment [10]. Of the 45 million aged persons living in the US, approximately 5 million of that number have been diagnosed with Alzheimer's [10]. This equates to 1 out of every 9 of the elderly population suffering from this disease. The Alzheimer's Foundation of America reports that the life expectancy for these individuals is generally anywhere from 8-10 years, with fewer than 3 percent of people living past 14 years post-diagnoses [11,12]. This timeline, however, is variable from person to person, and depends on the patient's age and overall health at the time of diagnoses. Some major factors of a person's survivability are their overall health and level of inflammation throughout their disease progression.

This review article will discuss the points of Alzheimer's and inflammation, and will talk about possible immune therapies to treat the inflammation causing the progression of AD.

Alzheimer's Diseases an Age Related Disease

Alois Alzheimer was the first to describe the hallmark pathologies within the brain of a demented patient in 1906, and these pathologies were later named after the psychiatrist who first described them, as Alzheimer's disease (AD). Although the history of this disease is more than 100 years, it has not been considered as major health issue until this century. It has developed into a problem for many nations. Although people are living longer lives, there is a larger population of elderly at risk for developing the disease. The patient population is increasing rapidly, and because of this so is the financial burden.

AD is an aging related disease. The cases which are associated

with earlier onset, which occur between the ages of 30-60, only makeup 5% of cases [13]; earlier onset can be caused by familial inheritance Alzheimer's (FAD) or by unknown causes. The cases caused by FAD are of autosomal dominant inheritance, and only represent 0.1% of total AD cases [14]. The genes affected in this case are related to the amyloid precursor protein (APP) gene on chromosome 21, and it is these mutations in APP that many of the therapeutic animal models are based on [15]. All other cases of Alzheimer's are referred to as sporadic AD, which make up 95% of the total disease cases, and it is seen generally in people over the age of 65. It is suspected that genetic and environmental risk factors play roles in the pathology.

In terms of testing for the genetic risk factors for late-onset AD, as of now there is that of the allele $\epsilon 4$ of the apolipoprotein (APOE) gene [16]. A variant in the gene can be found in 40-80% of all Alzheimer's cases [17]. For earlier-onset, there are various mutations, with most of them residing in the APP, Presenilin 1 (PSEN1; on chromosome 14), or Presenilin 2 (PSEN2; on chromosome 1) genes. Although testing for the APOE allele is available, it is not a determinant of whether you will or will not get AD, but merely increases a person's risk of ever developing AD if the abnormal allele is present.

As of now, there are no reliable prognoses for AD, and a patient won't know if they will ever contract the disease until they are experiencing the signs and symptoms. However, the signs between normal aging, AD, and dementia also have a lot of overlap. It is difficult to quickly discern one from the other. Getting old has its own features on the body, and tampering with retaining information and short term memory are among them [18,19]. However, when this progresses to a degree where the forgetting becomes more constant, and it gets to a degree where the patient doesn't even recognize that they are no longer retaining information, it starts to interfere with the patient's daily life. These are the early stages of dementia. According to the Alzheimer's Association, AD makes up about 60-80% of all cases of dementia. The two overlap until it can be difficult to pull out the diagnoses of AD from dementia. A full medical workup will be required to discern one from the other. No matter what factors have been uncovered, the biggest of all the risks is aging.

The Immune System Declines with Age

In addition to memory and the brain, the immune system also declines with age. This has been identified physically in the shrinkage of the thymus, in the loss of functionality of the appendix, and in the increasing instances of disease and infection in the elderly subjects. Older individuals also have a weaker response to vaccination compared to younger individuals [20]. This is caused by an inability to maintain the level of homeostasis previously preserved throughout earlier life. This too presents economic problems to the nation, as the group of people over the age of 65 is quickly growing and it is this group requiring more of the medical attention and funding. Their growing numbers are due, in part, to the fact that people are living longer with medical advances, and that the baby boomer generation is becoming of retirement age. This group will swell over the next 10 years, and will present a challenge to the current medical structure [21].

The immune system of our body can be classified into native, or innate, and adaptive systems. The innate immune system acts as natural defense, whereas the adaptive system requires priming and training in order to act against specific antigens.

There are studies stating that most of the innate immunity is preserved throughout the aging process [22]. One of the more interesting cell population to decline with age, and is part of the innate immunity, is that of dendritic cells (DC) [23]. These cells are the messengers between the innate and adaptive immune responses by presenting antigens to T cells, and thereby activate the adaptive immune system. Although the DC's function seems to be maintained throughout life [24-26], there is a drop in physical cell numbers. There are less antigens being presented to help T cells activity, simply because the body doesn't have the numbers. Due to this fact, aged subjects are more acceptable to pathogens that they once had protection from.

Changes in the adaptive immune system, such as those to B and T cells, also hinder our ability to maintain a healthy body in advanced age. The two most important aspects of the adaptive immune system are the 1) ability to have a massive repertoire of specific and diverse antigen-recognizing populations, or naïve lymphocytes, and 2) the ability to maintain populations of cells that have already encountered antigens months or years prior, and still have the ability to fight said antigens. As the aging process occurs, there is a notable decrease in the size of the thymus, which results in an overall decrease in the size of the naïve T lymphocyte population [27] and the loss of hematopoietic bone marrow causes a loss in naïve B cells [28]. Without a large population of naïve cells at later ages, the population of memory cells, formed against pathogens at earlier ages, begin to go through oligoclonal expansion with reduced antigen recognition [29]. These alterations result in changes to the normal levels of gene expression and to the amount of cytokines and signaling molecules released [30]. The system becomes more dependent on what defense has already been made and almost abandons the shrinking population of naïve cells, and as a result the body becomes more susceptible to new pathogens.

In patients with AD, the usage of the innate immunity can be seen in the aspects of phagocytosis and inflammation in the CNS. The microglial and astrocyte cells have some phagocytic ability in clearing the burden of the amyloid beta ($A\beta$) peptides, those aggregated forms thought to cause AD, from the CNS [31]. Thus, with the activation of the innate immune system comes widespread inflammation throughout the CNS. Inflammation can be seen by testing for various cytokines and chemokines on the brain in post-mortem subjects with AD pathologies [32,33]. However even when there is infection outside of the CNS, and this is especially common in the elderly, there is activation of the peripheral immune system and secretion of inflammatory factors. The cytokines produced peripherally are carried to the brain via the circulatory system, where the effects of these cytokines are reciprocated in the CNS [34]. This can increase inflammation in the brain, and lead to signs of depression and can exacerbate CNS disease.

The adaptive immunity also plays a role in the clearance of the A β deposits, and this can be enhanced through the immunization at a peripheral location with exogenous A β in mice [35,36]. However, it is unclear whether this works as well endogenously in the body, but it was found that T cells may have some intrinsic reactivity to the A β peptide, and that this reactivity may be increased with the increasing age of the subject [37]. When A β activated T cells were transferred into APP/PS1 transgenic mice, the mice can improve significantly in their behavior performance [38,39]. Some of the B cell and T cell epitopes of the A β peptide have also been elucidated [40,41], which provide evidence that the peptides may trigger responses normally in the body. When the A β vaccination trial moved onto human subjects, it was suspended due to some patients suffering from meningoencephalitis [42,43]. This side effect was suspected to be the cause of over activation of the immune system, thereby inducing inflammation. Many think this was caused by the adjuvant used to prime the immune system for the delivery of the A β peptide [44-47]. Since A β vaccination has been proven to prevent disease progression [48,49], other methods of delivery have been worked on in recent years. The initial end-goal ideas of the A β vaccine has remained the same, but the components of how to accomplish the end-goal have been altered, such as the method of vaccination (intranasal, intramuscular, subcutaneous, etc.) and what components to include in the vaccine (A β only, A β + adjuvant, other compounds to help initiate an immune response, etc.). It was found that anti-inflammatory cytokines, such as IL4, IL10, and TGF β , could be seen when A β was administered intranasally [37]. It is through this intrinsic activity of T cells that we can activate components of the immune system, without activating the mass pro-inflammatory cytokine reaction that causes widespread side-effect pathologies in the CNS.

Another large aspect of aging individuals is a low-level of chronic inflammation persistent in the body. This can be associated with an increase in free radical oxygen species or a decrease in cellular and mitochondrial function, or both. It has been long thought that oxidative stress plays a great factor in AD [50,51]. In the AD brain, there seems to be a higher concentration of iron (Fe) and copper (Cu) which can cause production of more free oxygen radicals to be produced by Fenton reactions, as well as increased levels of protein and DNA oxidation [52]. It is also thought that the neuronal membranes, and their oxidation by these free radicals, may be responsible for the conversion of monomeric A β into A β plaques and fibrils [53]. However free radicals and oxidative stress produce their effects, they are still believed to be a key factor in the progression of the disease [54,55].

Aggregated Amyloid Beta Presents a Problem to the Immune System

Although the function of amyloid beta (A β), a peptide made up of 42/43 amino acids, is not well understood [56], they are an endogenous component in the brain. This molecule is constituted to extracellular plaques, one of the hallmark in AD. The other trademark of the disease that Alois Alzheimer elucidated was the tau protein, or neurofibrillary tangles (NFTs) inside the

neuronal cells. Although the NFTs play some major role in AD, it is questionable how big that role actually is, as they are seen in many other neurodegenerative disorders [57-60]. For example, the transgenic mouse model of the disease, showing the amyloid cascade, does not exhibit the tau pathologies [15,61]. Studies have focused on changing the external amyloid plaques rather than changing the internal makeup of the cell to alter NFTs. In respect to A β , how is it that a peptide normally residing in the body throughout life can suddenly cause the pathologies of AD, and ultimately the deterioration of the brain? It comes from the combination of declining homeostasis, the decline in immune function, and the ability of the A β peptides to become larger plaques.

The A β 42 peptide is highly hydrophobic and sticky. It normally resides as a part of the amyloid precursor (APP) protein in the membranes of neurons, which are concentrated at the synapses. It is cleaved by 2 secretase enzymes (beta, and gamma) from APP, and when cleaved produces two isoforms—A β ₄₀ and A β ₄₂. The A β ₄₀ isoform is the most common in the body, but the A β ₄₂ is the more likely of the two to form oligomers and fibrils, which result in the amyloid plaques. Cleaved A β monomers are normally degraded by amyloid-degrading enzymes, such as neprilysin [62]. When two or more of these cleaved A β proteins come together, they form misfolded oligomers. These soluble oligomers have been shown to be synaptotoxic [63], and also serve as “seeds” that will eventually grow into bigger polymers of A β , which are the amyloid plaques found in the synapses [64]. When A β self-aggregates, it generates many isoforms that are harmful to the local neurons. It creates radical oxygen species [65], which in turn tend to cause lipid peroxidation of the neuronal membranes and cause the formation of reactive aldehydes [66]. These aldehydes go on to cause problems with ATPases, glucose and glutamate transporters, and eventually cause depolarization of the neuron. When the neuron depolarizes, it causes complications with neuron signaling and excitability, calcium influx, and mitochondrial function [67].

The immune system recognizes A β monomers as normal, so no immune response is mounted against it. However, oligomers and larger polymers are difficult to metabolize and clear. The different isoforms can confuse the immune system, and are seen as foreign to the body. This causes the activation of cells and mass inflammation to occur in the brain. The A β oligomers, seen as foreign molecular structures, activate the innate immune system through pattern recognition receptors (PRR). This inflammatory process goes on to cause the AD pathologies [68]. The idea of this malicious cycle of A β production and chronic inflammation is summed up in Figure 1. These additive structures of A β are recognized by microglial and astroglial cells in the CNS through the PRRs. The microglial cells are then able to phagocytize the A β [69] and store the peptide inside the cell, reducing the burden of building plaques, but it is unsure if the microglial cells have the capability to degrade all the isoforms of A β . In a study performed by Wyss-Coray, exogenous astrocytes could degrade A β without additional stimuli, whereas microglial required stimuli from various cytokines or opsonizing antibodies [70,71]. Even with

Figure 1: The animation shows the inflammatory cycle that takes place in the brain of patients with Alzheimer's disease. When the individual ages, there is the dampening of metabolism and clearance of A β peptide in the brain. These A β monomers, normally cleared from the body, may aggregate into oligomers, which then are seen as foreign and are phagocytized by astrocytes or microglial cells in the CNS [93]. These cells cause activation of the T cells, which both then go on to cause the release of pro-inflammatory cytokines [94]. There is a change in the T cell clonality of AD, and it seems to shift towards a CD4 response over a CD8 response [95]. As IL10 is inhibited in this process, the immune system is no longer suppressed and the CD4 inflammatory response is allowed to overtake the process. Lymphocytes from the T helper cell line (such as Th1, Th2, Th9, and Th17) are important in starting and maintaining inflammatory processes. Inflammatory cytokines such as IFN-gamma, TNF, IL-2, IL-4, IL-5, and IL-13 are responsible for these effects. The level of inflammation is increased in the CNS, and this is thought to increase the activity of the secretase enzymes [96-98]. If the A β oligomers are not cleared in time, they may aggregate further to form the amyloid plaques, which are the cause of toxicity to the neurons and local environment. These plaques are too big to be taken up by any of the antigen presenting cells (APC), and they will eventually cause the apoptosis of the nearby neuronal cells. Some molecules, such as melatonin [99], caffeine [100], and THC [101,102], have been shown to bind and alter either the secretases enzymes or the A β molecules themselves, thereby preventing aggregation.

these ongoing attempts to clear the A β , it is thought that the peptides aggregate while being moved around from cell to cell, or even within the cell itself, and that this aggregation during handling in turn causes neuronal toxicity and cell death [72]. The binding of A β oligomers and fibrils to other proteins within the environment, such as those containing sialic acid, can also cause the fibrils to be hidden or masked from the immune system [73]. Thus increasing the buildup of these components in the body without the immune system to recognize them. The chronic inflammation, caused by negative feedback through these PRRs, can dampen the sensitivity of glial cells to antigens, and induce immune tolerance of the A β peptide. This could in turn exacerbate and further progress the AD pathology.

Limiting the cytokines that produce the inflammatory

response can help alleviate the pathologies of AD. The development of small peptides promoting anti-inflammatory response, through the suppression of inflammatory cytokines, have been seen to be beneficial in immunomodulation [74]. Compounds, such as melatonin [75,76], caffeine [77-79] and THC [80], have been shown to prevent the aggregation of the A β peptides, and some have been shown to behaviorally benefit in the transgenic mouse model. It is worth mentioning that they all have the ability to modulate the immune system. This also implies that activation to immune system may cause improvement in the symptoms, pathologies, and cognitive impairment of the individual. The Current Status and Future of AD, and Immunotherapy as a Solution

In the US National Institute of Health database, there are

Table 1: Summary of potential immune targets in AD.

	Immune System Role	How affects disease state
IFN-γ	Activator of macrophages-pro-inflammatory; irregular expression associated with autoimmune disease	Activates microglia and cellular response in brain, increase inflammation, A β plaque burden in AD brain [103,104]
TNF-α	Induces inflammation and apoptotic cell death; produced mainly by activated macrophages	Levels elevated in AD [105]; Inhibition of TNF- α may aid in treatment [106]
IL-1	Increases movement of lymphocytes to site of infection	Aids progression of disease [107]; Receptor antagonist shows disease improvement [108]
IL-4	Induce differentiation of naïve T helper cells to Th2 cells; Stimulate active B cells/humoral response	Promote M2 cell formation, reduction of pathological inflammation; Upregulated in patients treated with AChE inhibitors [109]
IL-6	Pro-inflammatory cytokine	Cortical senile plaques display strong IL6 immunoreactivity; May be responsible for acute-phase state in AD [110]
IL-10	Anti-Inflammatory Cytokine; Down regulate cellular response, upregulate humoral response	Strong regulator of inflammation state [111]; polymorphism in IL10 promoter is a risk factor for AD [112]
IL-12	Induce differentiation of naïve T cells to Th1 cells; helps produce IFN- γ and TNF- α	Inhibition of IL12 signaling reduces AD pathologies and cognitive decline [113]
G-CSF (granulocyte colony stimulating factor)	Increase production of granulocytes and granulocyte-producing stem cells	May be reduced in early AD patients [114]; G-CSF treatment rescues memory impairment in mice [115]
Dendritic Cells (DCs)	Major antigen presenting cell to the body; Involved in innate immune response	Lack of DCs increases A β plaque in mice [116]; Possible vaccination route against A β [117]

Table represents possible immune targets in AD, their role in the immune system, and their disease implications.

Table 2: Summary of currently available therapies, approved and experimental.

Therapy	Approved vs. Experimental	AD Target	Clinical Findings
Cholinesterase Inhibitors (Donepezil, Galantamine, Rivastigmine)	FDA approved for various stages of AD	Prevent breakdown of acetyl choline in the brain—important for learning and memory	Slows cognitive symptom progression but doesn't seem to slow disease progression [118]
NMDA Receptor Antagonist (Memantine)	FDA approved to treat moderate to severe AD symptoms	Regulate glutamate activity and NMDA receptor activity—lessens excess glutamate and calcium into neuronal cells	Slows cognitive symptom progression but doesn't seem to slow disease progression [119]
Melatonin Treatment	Experimental	Inhibit A β aggregation; Seen to restore mitochondria function and lessen load of oxidative stress [75,120,121]	Greatly help sleep disorders and symptoms of sundowning, and to slow cognitive impairment [122]
THC Treatment	Experimental	Block A β production, disrupt A β plaque formation by binding to A β , and improve mitochondrial function at low doses [80]	Effects may be similar to melatonin and caffeine; studied little on animal models or humans
Caffeine Treatment	Experimental	Blocks β - and γ - secretases forming A β monomers [77,100]	Shown to help reduce cognitive impairment in the mouse model [123]
Young Lymphocyte Infusion	Experimental	Young blood shown to change the molecular, structure, and cognitive function of older mice	Young blood seen to reverse effects of aging in brain of mice [92]
Free Radical Scavengers and Anti-inflammatory Drugs (Vitamin E, selegiline, NSAIDs, etc.)	Experimental	Oxidative stress and free radicals in the AD brain	Some improvement in terms of A β deposition, inflammation, and symptoms [124,125]

Table represents possible treatments, approved and experimental, in Alzheimer's, as well as possible clinical and laboratory findings.

over 1,000 clinical trials that are currently ongoing testing the effects of compounds on AD. As of now, there are a handful of known strategies to slow or stop the pathologies of AD through intervention with the amyloid cascade. Many of these strategies, as well as most of the drugs that have been in previous clinical trials for AD, are based on the gamma or beta secretases in the body that deal with the creation of A β from APP. Halting or inhibiting these enzymes would drop the load on the CNS in terms of the building A β plaques. Many of the drugs working on these enzymes, such as Semagacestat, were discontinued in the second or third phases of clinical trials due to the low activity and low beneficial significance of the compounds. This leaves us with a remaining small pharmaceutical pool consisting of cholinesterase inhibitors and NMDA antagonists. These drugs work through altering the conditions in the brain, which overlap with the pathologies of AD, and they usually improve the conditions in the CNS to temporarily halt the disease progression. The activity of these drugs depends on the individual, and it is only for a temporary halt to progressing past the stage of mild AD.

Another strategy currently being studied is that of anti-aggregation molecules. These molecules, such as melatonin and caffeine, prevent the bunching of the A β peptides. These compounds tend to show the improvement of mitochondrial function in the cell, and also provide some degree of neuroprotection. Melatonin has even shown to cause improvement of neurogenesis in the hippocampus [81]. Although these compounds do provide benefits, these tend to be temporary in terms of AD and the progression of its pathologies. Though incorporating these molecules into the individual's diet, along with sufficient stimulation and exercise, seems to be particularly effective in halting the disease [82,83].

Immunotherapy has been showing increasingly substantial results in terms of treating AD over the last 10 years. The idea has been to stimulate the host immune system to recognize and eliminate the amyloid protein plaques or oligomers without causing any other side effects. It is simple in theory, but has been shown to be increasingly difficult to carry out. Immunization has been shown to produce antibodies to the amyloid peptide and to prevent the formation of the A β plaques. Previous vaccination with A β 42 has shown to reduce the number of plaques, but it has not halted the progression of the neurodegeneration [84]. Still, immunotherapy seems to be the way to move forward in terms of finding significant treatment or a cure.

One of the ways that immunotherapy might be helpful is by taking advantage of a process already in place. The stimulation of the systemic adaptive immune system, induced by A β , seems to be positive to the mice they have been studied in, in terms of the pathologies and behavioral changes [48,85]. It can be difficult, however, to prime the immune system to a specific or a couple of epitopes from A β . For example, insulin is made up of 51 amino acids, but has over 115 antibody epitopes on its surface due to all the overlapping domains of the amino acids [86]. Each epitope has approximately 15 amino acids in its sequence, where 5 of these amino acids strongly influence the binding ability of the

epitope to the epitope binding site on antibody or MHC molecules. One of the great things about the adaptive immune system is that it is so specific in response to the antigens presented. It may be that finding the right domain may be the answer to the problems associated with vaccination.

However, the problem with vaccination in aged subjects is that they have a weaker response to the peptide due to the dampened, aged immune system. The antibody response to an antigen in the elderly is smaller in number and dissipates faster [20]. This process, also known as immunosenescence, is the reason adjuvants, molecules such as aluminum salts, are required. The adjuvant keeps the antigen from dispersing from the site of injection, and begins to stimulate the innate immune response. It has been thought that the CNS inflammation that occurred from earlier AD vaccination studies was due to the adjuvant used in the vaccine [44]. Other types of immunization have been studied since then, such as mucosal or intranasal inoculation. However, these treatments required repetitive treatments regimens and only partially cleared the A β plaques [87,88].

Thinking of different forms of vaccination may be beneficial in terms of finding a cure, or even just to better understand the system. Harnessing the potential of a dendritic cell's (DC) ability to present antigens to the system is a possibility, and is currently being studied [89]. Taking a person's DCs, populating them, instructing them to uptake an antigen, and injecting these same cells into the person as a vaccine may be a feasible vaccination route in the future. With this process, there would be minimal chance for rejection of the vaccine, and the functionality of the DCs has been shown to be efficient throughout life, even in elderly populations. Though the amount of cells present in older individuals is less than that of their younger counterparts [90,91]. It could be that infusing large numbers of DCs, already having taken up an antigen, could provide substantial activation of the immune system to clear the body of said antigen, without causing the inflammation or other side effects.

In terms of a possible prognosis for AD, instead of manipulating the immune system, it may be possible to read the changes already written in the cell population of a person's immunity. There are enormous numbers of naïve T cells in the human body, each one waiting to respond a specific antigen. When the antigen matches up with the corresponding T cell, the T cell begins to replicate, thereby forming a population of clones to track out all the copies of the same epitope. If the epitope is represented on the A β peptide, and there is activation of the T cells, then the clones can be detected in the periphery in the system. The changes in the T cell receptor (TCR) can then be detected peripherally by exacting the patient's blood and examining the changes in TCR clonality. It may be that these changes can be detected with a level of accuracy, and that this level may represent a reliable prognosis to the changes in the body formed from AD.

The current idea for treatment is returning the immune system back to the image of what it looked like in youth. In one of the biggest clinical studies for AD, Wyss-Coray and his lab are going to infuse AD patients with young blood. In previous studies by his lab, the infusion of blood from younger mice recharged the

brain of the older mice [92], and they are hoping to replicate this result in humans. However, it may not be the entirety of the blood that we need; it may be just one or two components that were present at one point in adolescence, but are lost or functionally lessened as we age. Either way, Alzheimer's disease is a pathology of aging, and the key to unlocking this disease may very well be found in the youth.

Conclusion

The marriage between inflammation and aging is one that is ultimately detrimental to the patient, and it is a common factor in many of the highest disease mortality rates. As the patient's age increases, so does their risk for developing dementia, and possibly AD. Something that is commonly known is that when we get older, we become more at risk of developing disease and infection, which is a result of our declining immune system. We see that our immunity is highest when we are relatively young to mid-age, and from there we are trying to maintain this level of immunity from declining. A common theme in patients with AD is a dysfunction of the immune system and higher than normal levels of inflammation. Treating both of these will help us come to a reliable therapy to treat AD and other similar neurological diseases.

It is our thoughts, that through immunotherapies and neuroimmune manipulations, that we can treat a wide array of disease. With these new technologies, like immune cell infusion in elderly patients, DC vaccinations, and T cell receptor monitoring, we can effectively treat the disease and the changes the make to our body's watchdogs, the immune system.

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