Exploring the Role of Programmed Cell Death Protein 1 in Alzheimer's Disease Associated Autoimmunity

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "Exploring the Role of Programmed Cell Death Protein 1 in Alzheimer's Disease Associated Autoimmunity" submitted by Afsara Sumon Aana (16146032) of Spring 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors of Pharmacy on 15th December, 2020.

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Ethics Statement

This is to certify that this project titled “Exploring the Role of Programmed Cell Death Protein 1 in Alzheimer’s Disease associated autoimmunity” is submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.) from the Department of Pharmacy, BRAC University constitutes my own work under supervision of Md. Tanvir Kabir, Senior Lecturer, Department of Pharmacy, BRAC University and I have given appropriate credit where I have used language, ideas or writings of another

Abstract

Alzheimer's disease is the most common type of neurodegenerative disorder oriented dementia which is regulated by chronic inflammation in brain cells. Nevertheless, repeated experiments with immunosuppressive agents had failures to treat AD, implementing immune checkpoint blockade to affect the pathogenesis of AD showed some lights of hope in animal model. These animal trials stated about the mitigation of neuronal inflammatory responses and diminution in amyloid beta plaque formation and decrease in Tau protein entanglement. The cognitive symptoms were also observed as falling down. A massive surprising change in the tau pathology was informed by these researches that the macrophages were increased within neuronal parenchyma. In general, almost all the relevant experiments stated that PD-1 and ligand targeted immune checkpoint blockade can modify the factors which help to progress AD or cognitive behaviors. So this pathway can help to combat this disease succefully.

Keywords: Alzheimer's disease, Amyloid beta, Tau protein, PD-1, Autoimmunity.

Dedication

I want to dedicate this project to my respectable supervisor Md. Tanvir Kabir, Senior Lecturer, Department of Pharmacy, Brac University for his continuous guidance throughout my project.

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I would like to proceed by thanking the Almighty who is the source of our strength and knowledge which have enabled me to complete this project with full diligence.

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Table of Content

List of figures

List of Acronyms

AD	Alzheimer’s Disease
CVD	Cardio Vascular Disease
APP	Amyloid Protein Precursor
NFT	Neurofibrilary Tangles
APOE	Apolipoprotein E
PSEN-1	Presenilin-1
PSEN-2	Presenilin-2
DSM	Diagnostic and Statistical Manual of Mental Disorders
NINCIDS	National Institute of Neurological and Communicative Disorders and Strokes
ADRDA	Alzheimer's Disease and Related Disorders Association
MMSE	Mini-Mental State Examination
CAMDEX	Cambridge Examination for Mental Disorders
CIs	Cholinesterase Inhibitors
BBB	Blood Brain Barrier
NICE	National Institute for Health and Care Excellence
NMDA	N-Methyl-D-Aspartic Acid
NSAIDs	Non Steroidal Anti Inflammatory Drugs
PD-1	Programmed Cell Death Protein-1
NFT	Neurofibrillary Tangles

Chapter 1 Dementia

Alzheimer's disease (AD) is one kind of neuro-degenerative disease and a type of dementia. It affects behavioral activities, memory functions and thinking abilities. Now what is dementia? Dementia is an impairment or disorder in cognitions and behaviors of elderly people mostly who are above 65 years old. Oxford dictionary has an elaborated meaning of dementia as below "Dementia is a chronic or persistent disorder of the mental processes caused by brain diseases or injury and marked by memory disorders, personality changes and impaired reasoning". Some significant symptoms are noticed throughout the past years in patients going through dementia that affect their memory, thinking and social abilities and also it affects their normal daily life. Dementia is not a specific disease but some other brain diseases caused by injuries and brain disorders or even genetic dysfunctions give rise dementia in a person. Though dementia is something about loss of memory but only having memory loss does not signifies that the person may have dementia.

There are some classified dementias those vary from each other by leaving different kinds of symptoms or etiologies to the patients. They are termed as following disorders:

Vascular dementia: series of small strokes can cause vascular dementia. Also known as Multy-Infracted Dementia (MID): It is the second most occurring dementia after AD.

Parkinson's disease dementia: At least one year later of the diagnosis of Parkinson’s disease in patients, if there is a decline in the thinking or memorizing, then this condition is called the Parkinson’s disease dementia.

DLB (Dementia with lewy bodies): When special types of protein called lewy bodies deposits around neurons, this affect the thinking of patients. This condition is known as Dementia with lewy bodies.

Mixed dementia: When two or more different types of demential symptoms are observed, then the person is affected by mixed dementia.

Fronto-temporal dementia (FTD): dementia caused by shrinking of frontal and temporal anterior lobes is termed as Fronto-Temporal dementia

Creutzfeldt-Jacob disease: Usually inherited type of dementia. The disease progression is rapid and faster.

Huntington’s disease: When certain neurons and cells of spinal cord waste away, Huntington’s disease occurs.

Wernicke Korsakoff syndrome: This type of dementia causes when there is lack of vitamin B1 in brain cells.

Chapter 2 Introduction of Alzheimer's Disease

This is the most common type of dementia which is progressive in nature that can cause brain cells to be degenerated or wasted away and die. It is known to be the most common and familiar form of dementia and specified as a continuous and progressive decline in thinking, social and behavioral skills. It is also creates dependency so that a person becomes disable to function independently. There are some specific symptoms observed in patients with AD. In early stages patient can forget recent conversations and events. When the patient progressively moves to severe stages, a severe development in memory impairment happens and the patient may lose the ability to cope up with everyday tasks. Medicines that claim to be effective can temporarily minimize the symptoms or can maximize the person's work ability. Therefore, the person can be reduced with dependency on others and can perform some easy daily tasks. There are some organizations and programs those relentlessly work to support and help the people with Alzheimer's disease. The one fact that is not avoidable and is the major concern for the experts is there is no such medication that can completely deal with Alzheimer's disease that can alter the pathway of this disease process in the neuro-cells. Though the this disease is not a direct reason of death but in patients with advance stage of AD the death causes are malnutrition, dehydration or infections such as pneumonia which are the complications that rises from progressive decline in brain function.

Chapter 3 Global scenario of AD

3.1 Worldwide prevalence of AD

Alzheimer's disease is one of the most prevalent neurodegenerative diseases in the world, affecting around 47 million of people in the world. So it is assumed that it is the most common type of dementia. Experts stated that, over 60-80% patients with dementia are suffering from Alzheimer's disease. Though increasing age is one of the greatest assumed factors for this disease but it is not a common part of aging. Initially while the patients are in early stage the symptoms are mild but with time they show up severely. It is a worldwide concern that supports following facts:

Majority of the patients going through AD are 65 years old or above. Over 200,000 Americans below the age of 65 have decreased onset of AD. It is the 6th leading cause of death is US. On average a person can live up to four to eight years with this disease diagnosis but also elongate their living dependent to other environmental factors. Only 1-in-4 people

with AD have been diagnosed. Third world counties have greater rates than developed countries. Dementia and Alzheimer's are most common in Western Europe, second is North America. AD is least prevalent in some regions of Africa, mostly is sub-Saharan regions. 68% projects increase in the global prevalence and low and middle income countries will be increase with AD and other demential burdens within 2050. By the year 2050 it is statistically estimated that over 16 million of people will suffer from AD. In United States, someone develops AD in every 66 seconds. In US, proportion of Ad by age: 85y/o: 38%; 75-84y/o: 44%; 65-74 y/o: 15% and <65%: 4%. Mississippi has a higher rate of Alzheimer's mortality but this causative death is lowest in US. Among AD patients, 30% of the people have heart disease and 29% have diabetes.

3.2 Alzheimer's disease in Asia-Pacific region

Several reports informed that about 60% of patients with dementia are having AD in Asia. Also there are 10-20% of AD+CVD cases were listed from Asia-Pacific region. AD is one of the under-diagnosed diseases in Asia(Chen et al., 2016). Surveys showed that age-adjusted dementia (above 65 years) prevalence is much higher in some specific Asian countries such as China: <=5%, Japan has near 12.4% prevalence of AD, South Korea: 10.1%. This type of dementia is less prevalent in other Asia pacific regions such as India: 2.7%, Thailand: 3.4%, Sri Lanka: 4.0%(Kalaria et al., 2008).

3.3 Prevalence of Alzheimer's disease in Bangladesh

Though AD is considered as one of the great diseases causing death to a huge number of people worldwide, epidemiological data are not precisely reported in Bangladesh yet. Another fact is that, funds for conducting research are limited in such a developing country as ours. Additionally most of the population are in young group here, so within 20 to 30 years, the chances of getting people with AD will go higher.

Surveys found out some factors that can regulate AD rates in BD:

Smoking: Among the countries that lead in Tobacco consuming, Bangladesh is one of the tops. It is statistically found that Bangladesh is one of the top ten countries who are listed with high current smoking cases with 44.7%. Findings said that about 43.3% of adults who are aged 15 years or above use some kinds of tobacco or products made from tobacco in Bangladesh (Durazzo et al., 2014; Rahman et al., 2017)

Higher obesity rates: Every 1-in-5 adults are overweight in Bangladesh according to a global survey. Currently above 40% people are in the risk of being obese (Gustafson et al., 2004;

Mielke et al., 2010; Naderali et al., 2009) Other findings showed that there is alarming high rates of young age obesity amongst urban children from wealthy families (Rahman et al., 2017).

Chapter 4 Epidemiology of AD

Some general surveys conducted in 2015 showed that almost 46.8 million people are suffering from dementia all over the world. The number of new cases is approximately 30% higher than the cases that were presented in WHO report. The highest incidents were from Asia with 49%, Europe with 25% and America with 18% (Ueda, 2015; Wimo & Prince, 2010). East Asia and Africa have largest number of people with dementia (9.8 million) according to World Alzheimer's Report estimations. Europe is in second with 7.4 million people. It is being predicted that by the year 2030 this number may rise to about 74.7 million and by 2050 this will go to 131.5 million (Ueda, 2015). Epidemiologically it was states that Alzheimer's disease affects around 5% of people who are aged 65 y/o and 20% individuals who are in their 80s. This indicates this prevalence gets doubled every 5 years (Qi et al., 2019). Experts stated in World Alzheimer's Report 2015 that in Europe and America the incident rates of AD are highest with 80-89 years old people. This rate is higher in Asia among 75-84 years and in Africa among 64-74 years old people (Ueda, 2015). There is an increased AD prevalence each year in the military veterans. More specifically with them who already suffer, TBI (Traumatic Brain Injury), disorders related to post traumatic stresses or injuries that happened during military training/services (Weiner et al., 2013). About 23% of TBI cases were oriented from improvisation with explosives during the war of Iraq and Afghanistan (Fischer, 2011). People having mild to moderate TBI have 2-to-4 times higher risk of developing AD at increased ages than others (Plassman et al., 2000). Boxers have higher risk of demential development (Shively et al., 2012). 2012 census said that there is a substantial increase in elderly population. That means it is a clear indication to age index (Holcombe, 1933). This rate is about 51.8% in Brazil. Also 2000 census had a concrete data revealed 1.2 million of disease prevalence in the country. And 100,000 new cases are filed each year (Reitz et al., 2011).The overall costs of AD were 818 billion dollers according to World Alzheimer's Report 2015 and the increase was about 35.4% from the same report that was published in 2010. In 2018 this cost may rise to 1 trillion and 2 trillion in 2030 (Caroline dos Santos Picanço et al., 2018).

Chapter 5 Pathogenesis of Alzheimer’s Disease

Alzheimer's disease has over a hundred years of history but still researchers have no specific clarifications about its pathogenesis and also there are gaps in its healing therapies. Some microscopic markers can state some hypothesis and characterization/strategies of this disease pathogenesis. Some hypothesis markers that support Alzheimer's disease pathogenesis are:

5.1 Amyloid Beta Hypothesis

The amyloid beta (Abeta) fragments and neurofibrillary tangles are important markers for alzheimer’s disease, that are known as amyloid hypothesis. These deposits form when there is an alteration in Amyloid protein precursors (APP) cleavage in the membrane of neuron cells one end is in the cell & other end is outside the cell. APP has some significant functions like it helps to grow the neurons & amp; can repair itself like before after trauma or an injury. APP acts like other proteins such as it gets used and over time it can get broken down and lost or reduced. Normally it gets cut off by an enzyme called alpha and gamma secretase. These chopped up peptides are soluble & goes away. But when beta teams up with alpha then they leave APP unsoluble residues that is called amyloid beta. These residues bond together and form a clump of amyloid plaques. These clumps can be stayed between two side-by-side neurons that can cause interruption in signaling. Then brain functions like memory storing or signaling can be seriously hampered. These plaque scan start up an immune response and cause inflammation, that can damage surounding neurons. Amyloid plaque can deposit around blood vessels in the brain and cause amyloid angiopathy. Then vessels may get ruptured and cause hemorrhage (Caroline dos Santos Picanço et al., 2018; Liu et al., 2015).

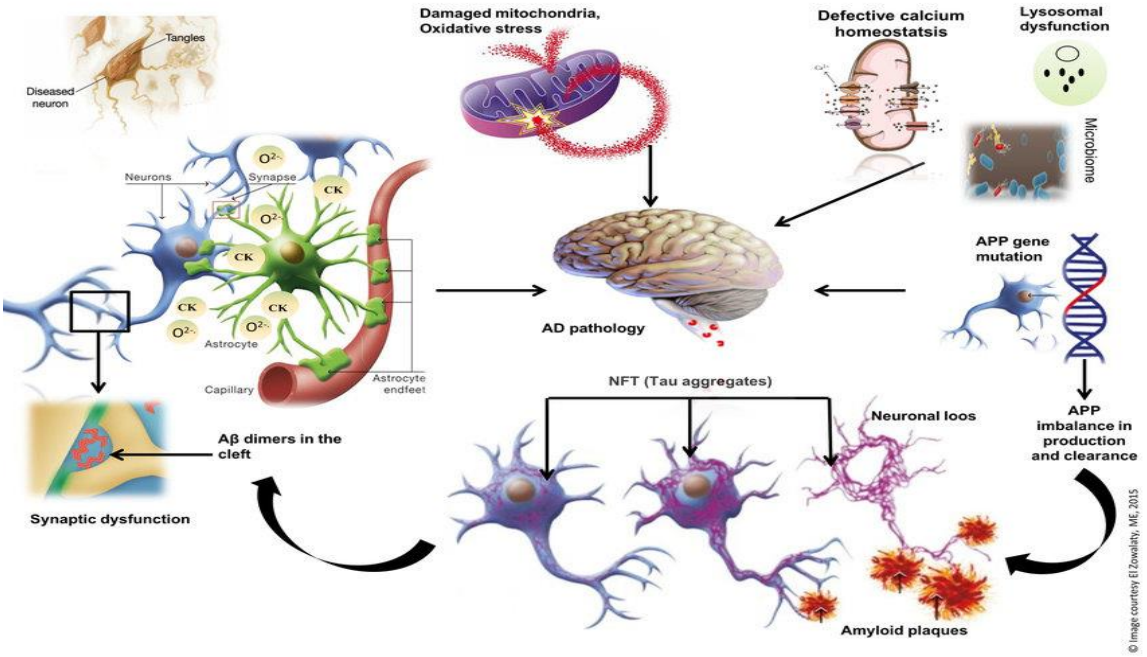

Figure 1: Amyloid beta plaque formation in AD progression (Marei et al., 2016)

5.2 Tau protein mechanism

Tau proteins are found inside the neurons cell. So this pathway is not similar and therefore opposing in some points with the beta amyloid plaque pathway. Neurons are held together by their cytoskeleton. This cytoskeleton is partly made up of microtubules. These microtubules help shipping nutrients/molecules along with the whole length of the cell. A special protein called Tau that is found inside the cells as previously mentioned makes sure that these transporting tracks do not lose their way and break the protein. A kind of assembly at tubulin thought that beta amyloid initiates pathways inside the neuron that leads to activate the kinase, an enzyme that has the ability transfer phosphate groups to tau proteins. Then tau protein changes shapes and stops supporting microtubules of clumps up together and gets tangled up. These are some specific findings in Alzheimers disease and termed as neurofibrillary tangles. Then microtubules can’t get signal and sometimes end up undergoing atrophy or even apoptosis or cell death(Caroline dos Santos Picanço et al., 2018; Oddo et al., 2006; Stancu et al., 2014).

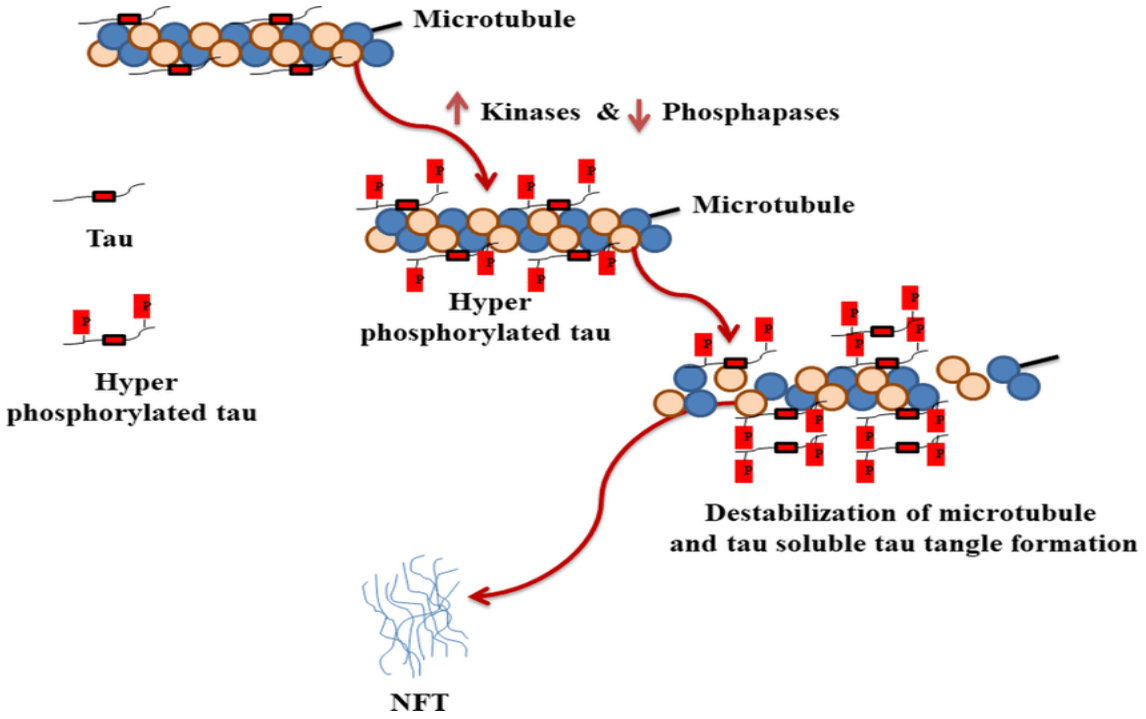

Figure 2: Tau protein entanglement during Alzheimer's disease progression (Kumar et al., 2017)

5.3 Genetic mechanism of AD

Alzheimer disease can be classified into two groups according to their genetic pathogenesis. They are termed as sporadic and familial.

Sporadic: It is something that is used to claim the late onset type, in where the exact cause is not very well defined yet and is probably a combined form of genetic and environmental risk factors. Most of the patients are in this type, in about 90-95% risk increases significantly with age, affecting around 1% of people age 60-65% and 50% of people who are 85 years old or over. The gene that is may be responsible is named as e4 allele of apolipoprotein E gene or APOE -E4. The risk of progressing Alzheimer's increases for patients who inherit one e4 allele and increases much more for patients who inherited e4 allele, one from each patients. Presence of APOE E4 allele indicates that patients are more susceptible to form beta amyloid plaques than normal people (Caroline dos Santos Picanço et al., 2018; Han & goleman, daniel; boyatzis, Richard; Mckee, 2019; Zhu et al., 2015)

Familial: Familial hypothesis is used to describe incidence where it is estimated that these dominant genes were inherited from parents, and have the ability to speed up the process of the disease progression. So sometimes familial is termed to indicate as early onset of Alzheimer's disease. This type of cases may account for 5-to-10% of the cases and can be

caused by several mutations in genetic cells. Mutations in the PSEN-1 gene of chromosome14 and PSEN-2 of chromosome1 have links to early onset Alzheimer's disease. Mutation in PSEN-1 and PSEN-2 can alter the point where gama secretase cleaves APP. This results in forming beta amyloid molecules which are more prone to be active at clumping up and producing plaques (Cai et al., 2015; Caroline dos Santos Picanço et al., 2018; Fetahu et al., 2019; Friedman et al., 2015; Huang et al., 2018; Karch et al., 2014).

Another estimated genetic reason of Alzheimer's disease is Trisomy21 or Down Syndrome, that may involve an additional pair of chromosome21. It is found that the genes responsible for producing APP are located on chromosome21. This means people with Down syndrome may have an extra pair of APP genes as well. So APP gene expression is prominent for them that may lead to have more amyloid beta plaques. For this specific reason familial AD appears at the age of 40 more often for people with Down syndrome (Caroline dos Santos Picanço et al., 2018).

5.4 Inflammatory mechanism and mitochondrial dysfunction leading to AD

Alzheimer's disease has links with inflammatory processes closely. Additionally various researches have already showed that Tau protein pathologies exacerbated while chronic or acute inflammatory processes occur. It is assumed that these inflammatory occurrences are promoted from microglial clusters that are located around the densest places of amyloid beta plaques and by microglial activation that can form neurofibrillary tangles. It is assumed that deposition of beta amyloid fragments and Tau protein pathology can affect mitochondrial activities in neuron cells. There is an impairment noticed in oxidative metabolism of mitochondria (Caroline dos Santos Picanço et al., 2018).

5.5 Cholinergic hypothesis

Cholinergic hypothesis is more studied hypothesis among the pathways that is related to evolution and onset of Alzheimer's disease. It is also considered as the evolution of the first theory regarding the pathogenesis of AD (Falco et al., 2015). Commonly AD carriers show atrophy, deficiency in central neurotransmission and synaptic loss. These terms were also described by histopathological markers. A neuron degeneration of basal forebrain is seen (Racchi et al., 2005). At initial stages, cholinergic loss in neurons of entorhial cortex and basal nuclease are noticed (Lunardi et al., 2013). But progressing to the advance stages, above 90% of cholinergic loss occurs. Regarding the cholinergic hypothesis, impaired or abnormal functioning of cholinergic system is responsible for inducing memory deficiency

that is similar to AD in animal testing models (Bartus RT et al., 1982). This hypothesis also states that neuronal cholinergic loss in basal forebrain and abnormalities in central cholinergic neurotransmission promotes cognitive appearance and cognitive symptoms is AD patients (Caroline dos Santos Picanço et al., 2018).

Chapter 6 Symptoms of Alzheimer's Disease

Commonly AD patients show three chronological stages of symptoms. In initial stages neuronal cholinergic impairment in limbic system, discrete memory loss, about 25% of hippocampus shrinkage (Seidl et al., 2010). The intermediate stage has longer duration and can last for two-to-ten years, and the symptoms are difficulties associated with communicating and recognizing people, decline in acetylcholin levels. When patient start progressing to the last stage difficulties increase. Patients become completely debilitated, and raise inability and dependency to perform daily tasks, degenerated cholinergic neurons promote destruction of stored memories, patient can completely forget his family, friends and pasts (Ballard et al., 2011; Bottino et al., 2002; Carvalho et al., 2016; Gross & Grossman, 2008).

Symptoms of AD become prominent as plaques of beta amyloid and tangles of Tau proteins accumulate and neuronal damages progress (Rosenberg et al., 2015). In initial stages, symptoms may not be noticeable. As it develops, patient forgets about short memories, as example he cannot remember what he had in his breakfast. Then they step to reduce motor skills making eating difficulties without support. Also language becomes hampered making it more difficult to keep conversations or even communicate. Eventually with progression he losses long term memories as forgetting his family members name and stepping forward to be disoriented. These symptoms may result to be dangerous as he easily gets wander from his home and gets lost. He becomes bedridden and cannot perform daily tasks without other's support. When the disease progresses, he becomes affected with severe malnutrition and eventually losses immunity. Then he becomes more disease susceptible and death happens (Caroline dos Santos Picanço et al., 2018).

Some other general symptoms are restlessness, apathy, hallucination, anxiety, depression, abnormalities in motor activity, delirium, sleep disorders, irritability, eating disorder, disinhibition or euphoria. Patients who develop AD in stage of dementia evolution can suffer from mood disorders. About 40-50% of AD patients can go through Depressive Symptoms but only 10-20% of cases can be affected by Depressive disorders. These Depressive

disorders are extensively studied as there are possibilities of neurocircuitry disorders. But still the depression related neuro-imaging data of AD patients are very few (Aggarwal et al., 2015; Alavijeh et al., 2017; Kerkeni et al., 2016; Rosenberg et al., 2015). Patients with advanced stages of AD can develop insidious and gradual cognitive deficit. Which may lead them to be disable and also compromise with the quality of life and progress to hospitalization, dependency and inevitable death (Haupt et al., 2000; Hughes et al., 1982).

Chapter 7 Conventional diagnosis methods of AD

It is essential to diagnose the patient while they are in their initial stages and have a well living condition (Caroline dos Santos Picanço et al., 2018). The criteria that are to be followed are from DSM IV (Diagnostic and Statistical Manual of Mental Disorders) and standards are established by NINCIDS (National Institute of Neurological and Communicative Disorders and Strokes) and ADRDA (Alzheimer's Disease and Related Disorders Association) are used (McKhann et al., 1984). To find the cognitive functions in patients, various psychometric and neuropsychological tests are required. Structural neuro imaging, functional and molecular neuroimaging, blood tests, EEG (Electroencephalogram), cerebrospinal fluid and evoked potentials are performed (Kim et al., 2005).

To get more complete vision genetic studies are also essential. Mini-Mental State Examination MMSE is one of the most practicing diagnosis methods in the world. This is a test that is established by NINCDA-ADRDA for global cognitive function. Association with other tools such as IMC (Information-Memory-Concentration) is highly appreciated (McKhann et al., 1984). ADAS-cog is an instrument that is use to estimate the cognitive frameworks of communication and language. Names of 15 figures in a black and white platform are applied by BNT (Boston Naming Test). It may also be designated in 8 figures in battery tests of the Abbreviated Neuropsychology (NEUROPSI) (Ostrosky-solís et al., 1999). NEUROPSI and CAMDEX are such test that may require the ability of relating three pairs of nouns regarding abstraction and conceptualization (Aprahamian et al., 2011; Roth et al., 1986).

Chapter 8 Current treatments of AD

8.1 Acetylecholinesterase Inhibitors

Acetylecholine levels are decreased in the brains of AD patients comparing with the normal beings. The function of acetylcholine is to transmitting the messages across the neurons. The availability of acetylcholine is enhanced by Cholinesterase Inhibitors (CI) if there is a case related to the disturbance of the memory. There are three classes of drugs that are being used in mild to moderate AD cases. They are Rivastigmine, Galantamine, Donepezil (Association, 2013). Rivastigmine and Donepezil can selectively inhibit whereas acetylcholine and butyrylcholinesterase both can be inhibited by Galantamine. Additionally there are no specific differences were observed in cognitive behavior and functions while dealing with rivastigmine and donepezil. As summary, all three drugs showed similar benefits(Birks, 2012). Although CIs cannot stop the progression of the disease, they still can show beneficial results for a long period of time. Besides, there are minimal side effects are noticed while dealing with CIs apart from those associated with the GI upsets. Hence, only cases like diarrhea, vomiting and nausea are reported. There is a complete guideline to use these drugs issued by NICE (National Institute for Health and Care Excellence)(Wirths & Zampar, 2020).

8.2 NMDA Receptor Antagonists

A widely used non-competitive NMDA receptor antagonist is Memantine that is beneficial for moderate to severe AD treatment. Glutamate induced excitotoxicity can be reduced by NMDA modulation. Several studies showed that NMDA associated treatment can successfully reduce the deterioration in AD patients. Additionally, patients require less service from caregivers and their agitations were reduced (Maidment et al., 2008). The use of Memantine was recommended by the NICE guidance [2011] as it is a part of NHS care for SEVERE AD patients. It was additionally mentioned that Memantine can also be a treatment way for moderated AD patients who refuse the CIs for their side effects (Bhushan et al., 2018).

8.3 Antidepressants and Antipsychotics

A very common obstacle in dealing with AD patients for the caregivers is the Behavioral and Psychological Symptoms of Dementia (BPSD). To a certain extent, Memantine and CIs can help to control or minimize these symptoms but during the period while the patients starter deteriorate, the effectiveness of these drugs seems insufficient. Both in the early and the late stages AD patients may suufer from depression. For countering these symptoms Tricyclic

agents, SSRIs (Selective Serotonin Reuptake Inhibitors), combination of noradrenergic and serotonergic inhibitors can be used. Various analysis showed that if these antidepressive drugs are discontinued is patients with AD, there was a sharp increase in depressive symptoms (Zec & Burkett, 2008). Quetiapine, Olanzapine, Risperidone, etc are some typically used antipsychotic drugs in AD patients. These drugs are also benefial for agitation though there is a difference in the doses (Cummings et al., 2016).

Chapter 9 Pro-inflammatory status in aging and effects of NSAIDs on Alzheimer's Disease progression

Numerous studies showed that there is a presence of irregular immune response in pathogenesis of AD. Though the fact is unclear that if the inflammatory processes are involved primarily or as a subsequent event, it is surely be stated that the flogistic processes are playing an important role in the progression of the disease. Some other studies showed that inflammation in elderly patients is asymptomatically low-graded and has the ability to constitute other age-related disease (Zotova et al., 2010). Some other studies demonstrated that age related cognitive decline, AD or other types of demential incidence have decreased prevalence with the patients who are treated with NSAIDs for a moderate or longer period of time. There was a reduced level of COX2 (Cyclo-Oxygenase-2) within the cerebrospinal fluid of the patients with last stage AD, although there was decreasing inflammatory markers induced by the pre-NSAID-treatments. Some epidemiological studies also stated that, there is a decreased AD prevalence with the patients who that anti-inflammatory therapies for a longer period of time due to have rheumatoid arthritis or autoimmune diseases (Zotova et al., 2010).

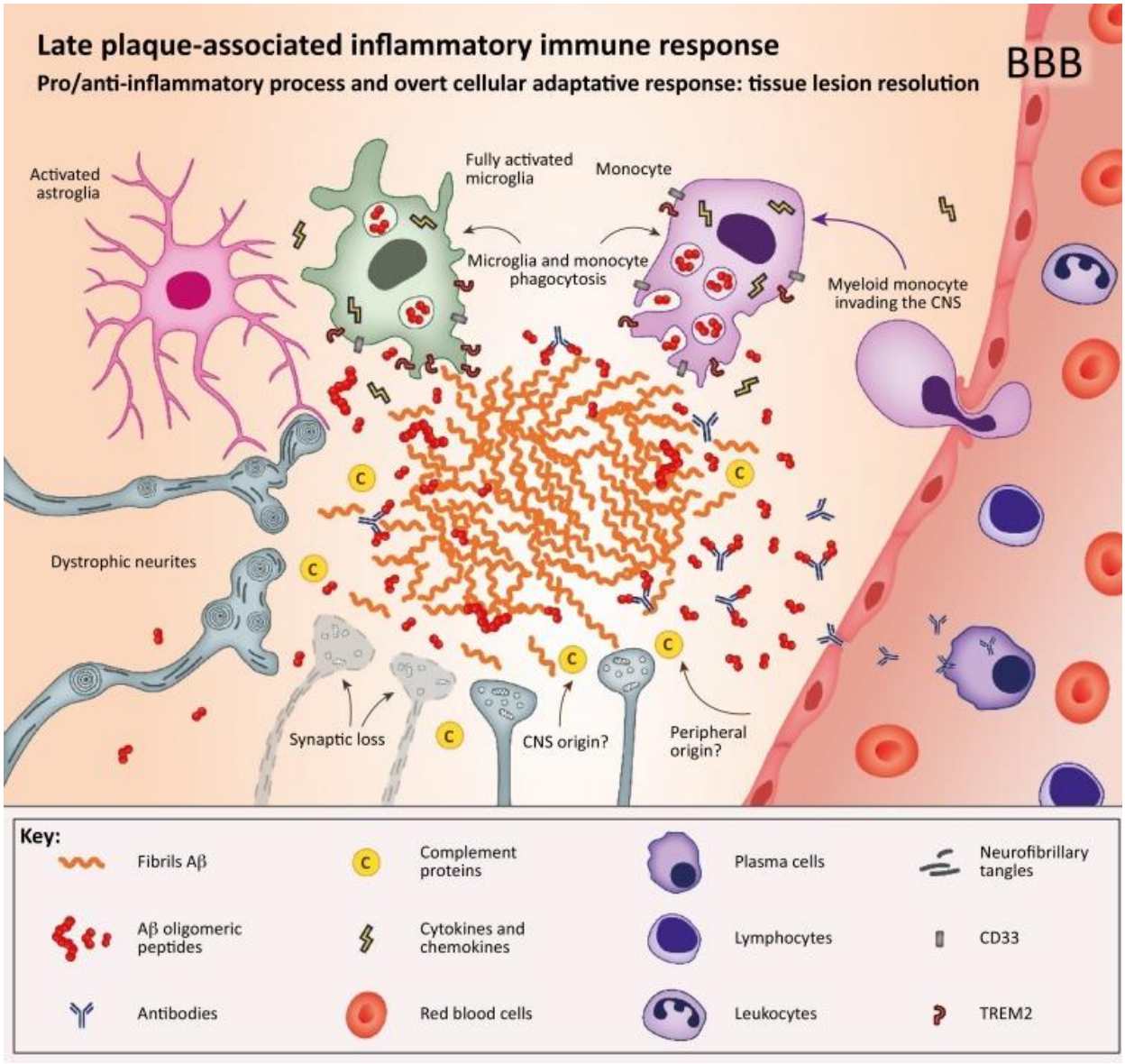

Figure 3: Proinflammatory immune response in end stage Alzheimer's disease (Cuello, 2017).

To sum up, it can be said that, neurodegeneration can be induced by pro-inflammatory molecules and thus memory loss, cognitive decline and dementia can be occurred. So, immunotherapy can be used as for both the therapeutic strategy and for the prevention (Sardi et al., 2011).

Chapter 10 Neurofibrillary pathology associated autoimmunity progression in AD

The neurons might not be killed directly by the autoimmune responses but they are able to make them vulnerable to the NFT pathology. We previously discussed that, the microtubule's destruction and the degradation of the neurons are caused generally by the NFT pathology. It is proved that apart from these hypothetic processes that are modulated by the adaptive immune system, intracerebral inflammation can be evoked by innate immune system as well. In early stages, the inflammation process starts with the generation of amyloid plaques. However, the inflammation travels to cerebral structures mediated memory signals and storage when the neuronal degradation progresses. Respectively, the inflammation spreads to normal tissues and generates chronic inflammation in brain. This process of mediating mal-adaptive innate immune system can be considered as the main reason for establishing a full-blown dementia in the last stages of Alzheimer's disease and also can cause death (Costanza, 2011; Falcon et al., n.d.; Mahar et al., 2017).

Chapter 11 Role of BBB and T lymphocytes in progression of AD

Researches show that BBB plays an important role to build a link between AD and the immune system. The brain is known as a sanctuary because it is isolated and protected from the reaction of other organism's immune responses by BBB. The primary function of BBB is to block the entry of foreign molecules such as immune-competent cells, immunoglobulins, etc into the brain. BBB become more permeable while compromising with inflammation, mirotrauma, microvascular pathologies and so on. This causes impairment in the immunological privilege of CNS. Some serum proteins show their presence in CSF of the brain after this incident (Querfurth & Laferla, 2010). When the BBB loses its integrity, it becomes easier for Aβ to enter and accumulate into the brain. Which lead to binding with astrocytes and priming the inflammatory reactions. Some acquisitions also believe that neurons have some autoantibodies that have the ability to start Aβ activities and deposition. As per previous discussions, Aβ also has the ability to initiate impairment in membrane potential, ATP production and electron transport system and causes mitochondrial poisoning (Sardi et al., 2011).

Another fact to be mentioned is that, T lymphocytes can pass BBB of AD patient's brain. So their numbers gradually increase significantly within temporal cortex and hippocampus in AD patients. They are widely expressed in MHC 1 and MHC 2 specifically in areas that show neuronal degradation that is typical in AD patient. to sum up, it can be said that, impaired

BBB is responsible to build a link between AD progression and T cells (Carr et al., 2009; Korolainen & Corporation, 2014).

Chapter 12 BBB dysfunction leading to the autoimmunity in AD

Dysfunction in BBB can be one of the major risk factors initiating AD. The proteins that function for memory signaling and adaptive immune system identifies them as non-self antigen, are harmed by an autoimmune response which is progressed slowly with the loss of brain's immune privilege. Some epigenetic foundation data of memory state a hypothesis about why the dysfunction in BBB evokes AD. The epigenetic processes mainly function by controlling the cell differentiation during the development higher organisms. There are possibilities for us to carry a huge variety in cell types as each type of cells shows the expression of specific gene sets. Epigenetic mechanism determines these specific gene sets. These epigenetic mechanisms are mediated by unique afferent signals in nervous system which can lead the functional and morphological differentiation of neurons. As formation of memory implies epigenetic mechanisms, it can be assumed that this process is similar to the cell differentiation processes. Comparing with other cell differentiation processes, the formation of memory is assumed to be modulated by the synthesis of unique types of proteins to memory engram brain cells (Bird & Bird, 2002; Boland et al., 2014; Smith & Meissner, 2013; Zhou et al., 2010). If this scenario actually happens, the proteins that uniquely work for memory functioning would be recognized by the adaptive immune system as non-self antigens as after the immune self-tolerance establishment the memory is generated. As per the discussion we can say, the damage or dysfunction in BBB can lead to progress to an autoimmune pathology against memory engram brain cells. This incident might be the leading cause for the brain immune privilege of BBB to isolate the brain from the immune system(Banks, 2014; Copyright & Vol, 2003).

Chapter 13 Role of Microglia in Alzheimer's Disease

Typically, it was considered that microglia is a bunch of resident immune brain cells whose initial function was to be responsive towards specific damage or infections. The dogma narrated that the microglia were either in an "activated" or in a "resting" state. Initially, it was assumed that the microglia may have multiple states of activation. They were termed as M1, designated as classically activated microglia and M2, designated by alternatively activated microglia. But further studies show that microglia never states in "resting". They perform an important role to balance homeostatic functions across the healthy brain cells that include the

key aspects in building memory and learning. When there is a sense of injury or damage, microglia progress to injury site to act a protective barrier between the injured and healthy tissue. Although, microglia have beneficial responses to injury, it can act harshly sometimes, specifically in situations like long term injuries or chronic inflammation such as AD (Holtman et al., 2015; Jansen et al., 2016; Miller et al., 2013).

The main aspects to target the microglia for the treatment of AD is to return the microglial phenotypes spectrum to the normal cognitive state from the disease condition. The mechanism is not is not t be to "turn off" the microglia by using broad anti-inflammatory medication, but to sharpen on specific regulators to precisely modulate phenotypes of the microglia. Currently some preclinical studies have supported this concept in mouse models having A-beta depositing brain condition. This experiment implied partial expulsion of the microglia by using CSF1R(Colony Stimulating Factor 1 Receptor) inhibitor that resulted in decreasing the total number of microglial cell. This process induces an ultimate shift in phenotypes of microglia into a more severe anti-inflammatory tone, which eventually suppresses the cognitive state in mouse model. Although a different gene expression was observes as a number of molecular phenotypes, which microglial phenotypes are to be modulated is not exactly identified (Wes et al., 2016).

Some other histological experiments gave statements that AD might be accompanied by microglial activation. AD is considered as a form of inflammation in brain, activation of microglia express Major Histo-compatibility Complex (MHC) class II molecule. MHC enable presentation of antigen to CD4+ T cells. This statement also shows that microglia may has a function as a tool in adaptive immune system (Almolda et al., 2011; City, 1988; Mcgeer et al., 2016; Working et al., 2000).

Chapter 14 Small molecules having negative impact on autoimmunity

CTLA4 and PD-1(Programmed Cell Death Protein-1) are two major receptors that can inhibit the immune checkpoint. They are readily expressed on immune cells and can mediate immunosuppressive pathway signals. CD28 and CTLA4 compete to bind with CD80 and CD86. CD28 and T cell receptors cannot get positive signals when PD-1 binds to PD-L1 and PD-L2 (Freeman et al., 2000). So the adaptive immune response is resisted by the suppressive behavior of these molecules. These immunosuppressive signal pathways are used to maintain a homeostatic balance in immune process. To add, these molecules are also considered to be useful in clinics. It is to mention that, the uses of various antibodies like

anti-CTLA4, anti-PD1 and anti-PD-L1 are widely seen in cancer treatments (Teng et al., 2018). This pathway showed a positive response in the history of cancer treatments though the field is still under experiment. Accordingly, PD1/PD-L pathway is considered to be an immune checkpoint based on this activity. T cells, B cells, some of the non-lymphocyte tissues and antigen-representing cells are precisely marked where PD-1 and its ligands can be expressed. Ligands of PD-1 can bind to the surface of T cells and mediate an inhibitory response in immune system. Additionally, PD-L1 can be expressed on pancreatic islets, placenta and cardiac endothelium. This indicates that PD-L1 has a role on immunological tolerance (Chinai et al., 2015). Apart from this, PD-1 has an extra ligand known as PDL-2, though the activities of PD-L1 are not as prominent as PD-L2. PD-L1 and PDL-2 have similar inhibitory activities but PDL-2 play different roles in compare to PD-L1 while functioning with T cell (Latchman et al., 2001). PD-1/PD-L pathway may also have contributions to regulate infectious mechanisms as they are involved in immune evasion by pathogens (Wykes & Lewin, 2017). Additionally, some experiments by using animal testing have stated PD-1 and PD-Ls are crucial to regulate autoimmunity and peripheral tolerance (Kuol et al., 2018). From the data of these studies it was stated that PD-1 and PD-Ls may have other definite functions apart from their role in the treatment of cancer (Qin et al., 2019).

Chapter 15 Role of PD-1 in diminishing autoimmunity

PD-1 and its ligands are associated with balance of both peripheral and central tolerance (Nishimura et al., 2000). Although numerous examinations show interesting inhibitory impacts of PD-1 ligands on immunological reaction, hardly any investigations characteristic an activatory part to these particles (Latchman et al., 2001). Subsequent discoveries extensively suggest PD-1 function in the acceptance and additionally support in immunological responses (Schools & Clinic, 1999; Tseng et al., 2001). Inhibitory signs produced by PD-1 and PD-L1can control both the central and the peripheral tolerance through different components. Developing thymocytes express both PD-1 and PD-L1 on their surface throughout central tolerance measure. PD-L1 is communicated comprehensively on the thymus, while PD-L2 articulation is restricted only to thymic medulla. PD-1 articulation on CD4+ CD8+ thymocytes is started as they go through TCRb reworking to show useful pre-TCRs on the surface of the cells. PD-1:PD-L1 communications restrain positive determination during the maturational stage of CD4+ CD8+ (DP) from DN. PD-1 signaling changes positive determination limits, and as an outcome of the PD-1 or PDL1 misfortune,

the quantity of DP thymocytes was précised to be increased. PD-1 is engaged with guideline of negative determination and has been distinguished as an applicant quality in a microarray examination of abnormal central resilience in non-corpulent diabetic (NOD) mice (Brown et al., 2020; Liang et al., 2003). As summary, these discoveries highlight a part for the enlistment of PD-1 and PD-L1 in central resistance. PD-1/PD-L pathway similarly assumes a basic part in giving tissue resilience. Self-reactive T cells getting away from the negative selection and ingoing the peripheral region, are constrained by peripheral resilience systems. PD-L1 and PD-L2 articulates on dendritic cells (DCs) and this incident could similarly has a part in the destiny of the regulation of T cells, deciding initiation or resistance by repressing self-reactive T cell reactions. Arising confirmations propose that juvenile DCs inspire resistance in T cells, and absence of PD-1 on antigen specific T cells expands CD8 T cell reactions to antigen-bearing resting DCs (Zamani et al., 2016).

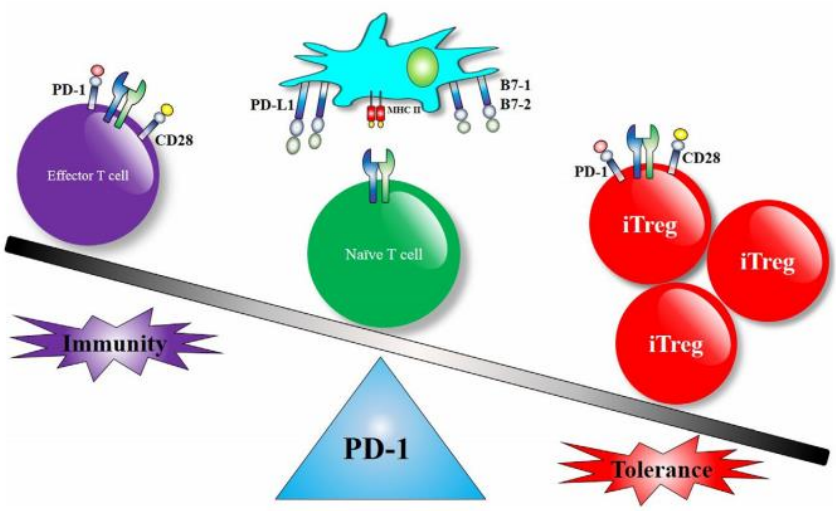

Figure 4: PD-1 functioning against T-cell responses (Zamani et al., 2016).

Chapter 16 Role of PD-1 in chronic inflammation

In progression of chronic inflammation, PD-1 on T cells collaborates with its ligands, those are discovered to be increased in macrophages, monocytes, and neutrophils, closing down the reaction of T cell and prompting immunosuppression. CD4+ type T cells communicating PD-1 during HBV contamination seemed to display decreasing work of assistant T cells, and after experimental treatment with PD-L1 bar, the capacity of CD4+ type T cells was mostly reestablished. PD-1 and consolidated bar of costimulatory atom OX40 (CD134) similarly exceeded the capacity of the HBV-explicit CD4+ type T cells. As of late, scientists found that during adenovirus and LCMV contamination, hepatic-inhabitant NK cells (LrNK)

communicating PD-L1 can control T cell antiviral action in liver. Moreover, barricade of PD-L1 can abrogate theLrNK cell associated antagonistic impact on T cells. Remarkably, PD-L1-communicating neutrophils ought to stand out for their significance in adding to T cell fatigue since they are substantially more various than other safe cells. Also, late examinations have indicated a connection between PD-1/PD-L1 articulation and clinical results. In severe and chronic diseases, up-regulation of PD-1 articulation was connected to diminished viability of CD4+ T cell antiretroviral treatment (ART). PD-1 articulation on CD8+ T cells after ART has been related with debilitated CD4+ 413 T cell safe reconstitution, microvascular infections and a decreased chance to viral bounce back after ART suspension. While the intense provocative period of constant HBV progresses, raised articulation of PD-1/PD-L1 is needed to counterbalance the expanding positive costimulatory signals to keep extreme harm from an over-energetic resistant reaction. While experimenting with Listeria-tainted mice, it was found that PD-L1 Provisional 16 ties to obscure receptors (not PD-1 or CD80) and is described as a costimulatory factor for antigen-explicit CD8+ type T cells. PD-1/PD-L1 inhibitors can re-fortify depleted T cells.

During LCMV contamination, PD-1/PD-L1 pathway barricade can reestablish infection explicit CD8+ T cell capacities, advancing expansion, cytokine creation and murdering limit. Moreover, PD1/PD-L1 pathway mechanism can lessen the viral effects. Reliable with these inventions, investigations of HIV and HBV/HCV contamination demonstrated comparable outcomes (Barber et al., 2006; Fuller et al., 2013; Zumla et al., 2016). What's more, scientists have announced that PD-1 is needed for keeping up T cell depletion, however PD-1 inhibitors can improve depleted T cell work (Vertès, 2020). Along with these lines, the circumstance of PD 1/PD-L1 pathway regulation is basic. Notwithstanding reinforcing T cell reactions, treatment associated with the hostile to PD-1 immunizer increased B cell reactions in a non-human primate model carrying HIV disease. In accordance with this finding, the blend of Tim-3 and PD-1 inhibitors re-animated depleted CD8+ T cells and diminished the viral burden in a mouse model of ongoing disease. Intriguingly, sometimes, PD-1 bar previously re-established infection explicit CD8+ T cell work, yet CD8+ T cells thusly became depleted once more, showing protection from PD-1 immunotherapy. Studies already have indicated that during the progression of chronic inflammations, T cells that are sensitive to PD-1 inhibitors are considered as "progenitor like" subsets, and the "terminally differentiated ones" are the less delicate subsets (Qin et al., 2019). Progenitor resembling T cells can change into

“terminally differentiated” T cells through expansion, which may clarify the above surprising results (Hoffmann et al., 2016; Shive et al., 2016; Sinha et al., n.d.).

Chapter 17 Role of PD-1 in Alzheimer’s disease associated Autoimmunity

Patients who have mild cognitive impairment or a condition of Alzheimer's disease express declined level of PD-1 on CD4+ T cells and decreased level of PD-L1 on CD14+ macrophages (Saresella et al., 2012). With the interruption of the PD-1/PD-L1 pathway, the arrival of IL-10 is also diminished. It is realized that IL-10 can improve pathology in animal models carrying AD, showing that the attenuation of AD is, at any rate partially, because of the PD-1/PD-L1 pathway. Notwithstanding, the sub-atomic and cell systems of the PD-1/PD-L1 connection in AD and the impact of this association on resistant cells in the CNS should be additionally examined. PD-L1 can similarly fill in as an endogenous agony inhibitor and a neuro-modulator. It can also be communicated in the spinal cord, dorsal root ganglia (DRG), nerves and skin. In guileless mice, PD-L1 can apply a pain relieving impact by collaborating with PD-1, then again, PD-1/PD-L1bars evokes mechanical allodynia (Koronyo-Hamaoui et al., 2009; Qin et al., 2019).

17.1Molecular pathway based on animal data indicating the effect of PD-1 on the pathogenesis of AD related autoimmunity

Inhibitory checkpoints of the immune system limit the action of memory T cells, chiefly those coordinated against self-compounds, to keep away from immune system infections. Among such checkpoints are the modified cell demise protein 1 AD is a staggering age-related neurodegenerative issue, and the most incessant reason for feeble dementia, an individual from the B7-CD28 family, communicated by an assortment of actuated effector memory resistant cells, including CD4+ T cells. The PD-1 ligand is communicated by the dendritic cells and administrative T cells, just as by non-immune cells, for example, astrocytes and epithelial and endothelial and cells. The cooperation between PD-1 and PD-L1 stifles memory T-cell reactions, including multiplication, and cytokine creation. Impeding the PD-L1/PD-1 pathway possibly brings about an expansion in T cell enactment (Ansari et al., 2003; Fife et al., 2009; Gotsman et al., 2007; Pittet et al., 2011; Yang et al., 2009). In light of some new arrangement, experts imagined that focusing on fundamental PD-1/PD-L1 may be an approach to initiate quite a defensive/reparative insusceptible reaction. Some investigations utilizing hostile to PD-1 or against PD-L1 immune response in the 5xFAD mouse model of Alzheimer’s disease, just as in a dementia model of tau pathology,

uncovered that such medicines are compelling in aiding and in any event, turning around intellectual hindrances and diminishing the pathology of the disease. This cycle was related with monocyte-inferred macrophages functioning to the memory. These macrophages locally express various atoms scavenger type receptors for expulsion of dead cells just as mis-folded or accumulated proteins, mitigating cytokines, and development factors. Critically, a solitary infusion of immune response coordinated against either PD-1 or PD-L1 started a chain reaction that began outside the cells of the brain, and prompted adjustments in a few cycles inside the cerebrum that together brought about infection alteration. Additionally, treatment implementing the PD-1 blockade pathway experimentally resulted in a reduction of cerebral loads of Aβ plaque in two different mouse models carrying moderate stages of AD. Besides, to get a long-term beneficial impact, repeated administration sessions were crucial. It also found that these experiments supported a protective role of the neurons from the autoimmunity mechanism for T cells (Baruch et al., 2016). Outstandingly, in most mouse models of AD, side effects of the disease start prior in females than in males. In people there is no unmistakable logical statement with respect to sexual orientation contrasts in AD, however most examinations have indicated that people display contrasts in the turn of events and movement of the infection. For the most part, female mice are considered at more serious danger and show more quick movement. Prominently, tau-driven models of dementia and amyloid-β driven pathology associated both female and male mice correspondingly reacted to treatment with safe checkpoint barricade coordinated to PD-1 or PD-L1 (Baruch et al., 2015, 2016; Marsh et al., 2016; Rosenzweig et al., 2019; Schwartz et al., 2019)

Chapter 18 Methodology

Around one hundred and fifty journal articles related to the autoimmunity progression in patients with Alzheimer's disease were studied through PubMed and Google Scholar. The articles that are written in English were the only priorities here. The key words that were used to search the related articles are- "Alzheimer's disease"; "Autoimmunity", "Programmed Cell Death-1" etc.

Chapter 19 Discussion

Numerous experiments have significantly stated about the clinical roles of anti PD-1/PD-L1 pathway promoting immunological incidents that happen in both outer region and in diseased condition of the brain. It also helps to maintain immunological relationship between the immune system and the brain. The changes observed in the immunological circumstances of

the brains of such animal models in various experiments were leading to a decrease in cognition. Specifically, it was found that in the animal models of AD, medication with the PD-1/PD-L1pathway that was targeted by immune checkpoint blockade drives a leukocyte trafficking to generate systemic immune response. Treatment with this pathway successfully reversed the pathology of the disease in animal models. These researches successfully proved that targeting PD-1 pathway that is related to the immune checkpoint blockade can have improved cognitive symptoms as it hat ability to modify the disease pathology. These experiments also displayed some modification in the immunological tolerance in the Animal model. Notably, PD-1 associated treatment as a blockade of immune checkpoint let not to target a single etiological factor of AD, rather this pathway is meant to affect the whole immune system to normalize the pathology of the brain.

Chapter 20 Conclusion

To conclude, data acquired from animal models suggests that PD-1 blockade pathway can evoke some immunological responses which start from the outer region of the brain and also affect the inflammation processes that are mediated from the impaired brain. This pathway can restore the interaction between the immune system and the brain. The changes in the modification of immunological responses of the brain result in the culminated reduction of cognitive symptoms and the manifestation of the disease pathology.

Chapter 21 Future work

Clinical trials and human based experiments with the implementation of PD-1targeted immune checkpoint blockade are still on demand to understand the proficiency and longevity of this pathway. Additionally, AD pathogenesis occupies almost the whole physiology of the patient, so targeting only a single immunological pathway may not be able to help the cognitive symptoms to a maximum extent. Also whether this treatment method can benefit as an anti-inflammatory therapy to the whole systemic pathway uniformly or not is still unclear. Notwithstanding, these preclinical data are still under further researches, successful attempts are encouraging enough to make interests in combined drug delivery in order to diminish the effects of AD.

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