Structural analysis of myeloid microglial cell surface antigen CD33 in the context of Alzheimer's disease

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INTRODUCTION

Alzheimer's disease is an irreversible, progressive brain disorder that destroys memory, thinking skills and ability to carry the simplest tasks. In brain, many abnormal clumps of BETA-amyloid (plaques) and tangled bundles of fibers (neurofibrillary, tau protein) (fig:1).Plaques are deposits of a protein fragment called BETA-amyloid, that builds up in the spaces between nerve cells. Tangles are twisted fibers of another protein called tau that build up inside cells, causing destruction and death of nerve cells. Other cells in the brain such as Astrocyte and Microglia clear a way to make the neurons healthy. The chronic inflammation sets in as the microglia cells that fails to clear away the fibre and astrocyte are stressed to react the microglia and eventually the neurons losse their ability to communicate and the brain shrinks, memory loss, impaired decision making, language problem (fig:2). Time for diagnosis to death for 80yrs old-3 or 4yrs, younger-10 or more. In U.S approximately 5.5 million people are affected and the prevalence worldwide is estimated to be as high as 24 million. Medication for mild to moderate is Cholinesterase that prevents the breakdown of acetylcholine, a brain chemical believed to be important for memory and thinking. Others are Razadyne (galantamine), Exelon (rivastigmine), and Aricept (donepezil). Medication to moderate to severe is Namenda (memantine) and N-methyl D-aspartate (NMDA) antagonist. Also the combination of Namenda & Aricept, Namzaric (donepezil & memantine). Current drug research in lead that targets tau protein 'AADvac1 is a vaccine has the potential to help stop the progression of alzheimer's, it is not been novel medication approved since 2003. And targeting the BETA-amyloid 'Aducanumab' is in research it slows the neurodegeneration and disease progression if successful it is released in march 21 2021.

Protein- Myeloid cell surface antigen CD33 [also known as Sialic acid-binding Ig like lectin 3(SIGLEC-3)]; plays a role in mediating cell-cell interactions and in maintaining immune cells in a resting state. preferentially binds to alpha 2,6-linked sialic acid. In the immune response, may act as an inhibitory receptor upon ligand induced tyrosine phosphorylation by recruiting cytoplasmic phosphatase via their SH2 domain that block signal transduction through dephosphorylation of signaling molecules.Induces apoptosis in acute myeloid leukemia(in vitro).One of the repressive effect of CD33 on monocyte activation requires phosphoinositide 3 kinase/P13K(fig:3).

Structure analysis-

Assembly composition:monomeric
Macromolecule:myeloid cell surface antigen CD33
Chains:E,F,G,H
Length:127 amino acids
Theoretical weight:14.65KDa
Source organism: *Homosapians*
Expression system: *Escherichia coli*
Gene names: CD33, SIGLEC3
Structure domains: Immunoglobulins.

EXPERIMENTALS

In order to understand the overall structure of the myeloid microglial cell surface antigen CD33, a 3-dimensional structure is been performed using pymol software in computational biology(PDB ID:- 6D48). For a good X ray crystal structure the difference between R work & R free should be less than or equal to 5%(0.212-0.176=0.036). The R work value should be roughly equal to resolution, resolution/10(1.78/10=0.17). Therefore the structure is passed both the test and it is less than 5%. The analysis of the structure includes alpha helix and beta strands by secondary structure in pymol (figure:4). The ligands are absent in cell surface receptor.

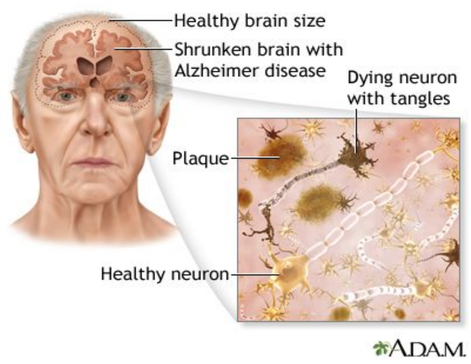

Figure 1:- Image of Shrunken brain due to dying neurons causes Alzheimer's disease.

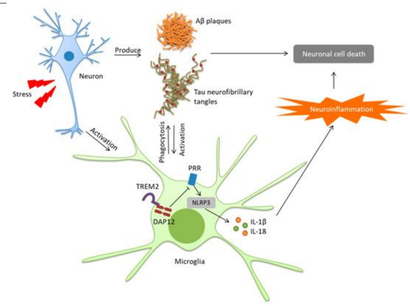

Figure 2:- Mechanism of Microglia induced neuroinflammation in Alzheimer's disease.

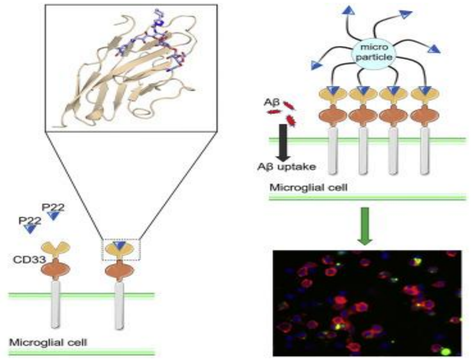

Figure 3:-Small molecule binding to Alzheimer Risk factor CD33 promotes Alpha Beta Phagocytosis.

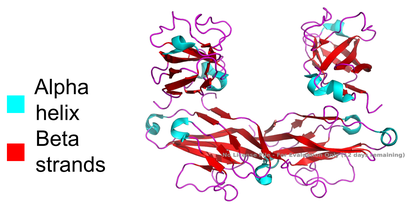

Figure 4-The 3-dimensional Structure of myeloid cell surface receptor, Alpha Helices and Beta strands.

RESULTS & DISCUSSION

The structure of myeloid microglia cell surface receptor (PDB ID:-6D48) contains 10 Alpha-helices and 3 Beta strands that form a sheet. It doesn't show ligands. The microglia act as protective cells, but may become inappropriately reactive in alzheimer's disease to drive neuropathology. Under the pathology of AD, the accumulation of amyloid-beta plaques and tau neurofibrillary tangles induce microglial M1- like activation, which produce inflammatory cytokines and cause neuronal cell death. Meanwhile, m2- like microglia is able to reduce Alpha Beta plaques and tau neurofibrillary tangles accumulative by phagocytosis. Glial-mediated inflammation is a 'double edged sword', performing both detrimential and beneficial function in AD. Dispite tremendous effort in elucidating the molecular and cellular mechanisms underlying AD pathology, to date, there is no treatment that could prevent or cure this disease. Current treatments are only useful in slowing down the progression of AD and helping patients manage some of their behavioural and cognitive symptoms.

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