CD33 and Alzheimers Disease: from Biology to Therapy

https://neurodegenerationresearch.eu/survey/cd33-and-alzheimers-disease-from-biology-to-therapy/

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USA

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Research Abstract

DESCRIPTION (provided by applicant): Preservation of cognitive abilities is one of the major medical challenges of the 21st century. Our current inability to prevent or delay Alzheimer’s disease (AD) and the expected increase in the prevalence of AD are predicted to give rise to a global AD pandemic. We have recently identified a novel pathway for amyloid beta

(A?clearance in the aging brain that is highly relevant to AD pathogenesis. In a very large family-based genome-wide association study, we identified CD33 as a novel late-onset AD risk factor. CD33 encodes a transmembrane sialic acid-binding immunoglobulin-like lectin that regulates innate immunity. We found that CD33 is specifically expressed in microglial cells and exhibits an increased expression in AD. The minor allele of the CD33 single nucleotide polymorphism rs3865444, which confers protection against AD, was associated with reductions in both CD33 expression and insoluble A? levels in AD brain. Using microglial cell cultures, we found that CD33 inhibits uptake and clearance of A?, a process that requires the sialic acid-binding domain of CD33. Finally, CD33 knock-out led to a marked reduction in insoluble A? levels and amyloid plaque burden in mouse models of AD. Thus, CD33 activity in microglial cells promotes A?athology by inhibiting A?ptake and clearance. Here, we propose to: 1) identify and characterize novel CD33 mutations linked to late-onset AD; 2) dissect the molecular mechanisms underlying the function of CD33 in microglia; and 3) inhibit CD33 activity for therapeutic purposes. In Aim1, we will analyze whole genome sequencing data from 410 families (1376 subjects) to identify novel CD33 mutations linked to AD. We will then examine the impact of these mutations on multiple pathological indices of AD in a cohort of 150 AD cases (K99). The most promising CD33 variants will be functionally characterized in microglial cells (R00). In Aim 2, we will define CD33-mediated signal transduction pathways in microglia. We will express mutant CD33 versions in which specific domains or predicted phosphorylation sites have been removed or mutated and assess their effects on the microglial transcriptome and A? clearance (K99). We will also identify CD33-interacting proteins in vivo using mass spectrometry. To explore the functional interaction between CD33 and TREM2 in microglia, we will use genetic analysis in microglial cell cultures (R00). In Aim 3, we will define the cellular signature of CD33 activity in microglia by characterizing the transcriptome of adult microglia isolated from mouse models of AD in which CD33 has been genetically inactivated (K99). We will also determine whether CD33 genetic inactivation restores cognition in mouse models of AD. Finally, we will develop and validate effective CD33 inhibitors by screening i) custom-synthesized sialic acid-based antagonists and ii) CD33-specific antibodies for their ability to inhibit CD33 function in microglial cell-based assays. Successful inhibitors will be further tested in mice (R00). Collectively, these studies might provide critical insights into a central pathway fr A?learance in the aging human brain and might result in a novel and powerful therapeutic approach for AD.

Further information available at:

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