CD33 in Alzheimer's Disease – Biology, Pathogenesis, and Therapeutics: A Mini-Review

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Abstract

Alzheimer's disease (AD) affects nearly 50 million people worldwide, and currently no disease-modifying treatment is available. With continuous failure of anti-amyloid-beta- or tau-based therapies, identification of new targets has become an urgent necessity for AD prevention and therapy. Recently, conventional genetic approaches and computational strategies have converged on immune-inflammatory pathways as key events in the pathogenesis of AD. A number of genes have been highly linked to the onset and development of late-onset sporadic AD, the most common form of AD. Strikingly, most of these genes are involved in microglial biology. Mutations and/or differential expression of microglial receptors such as TREM2, CD33, and CR3 have been strongly associated with an increased risk of developing AD. The mechanistic actions of these risk factors in AD etiology have been actively investigated since they were identified. Whether these genes can be targeted for a disease-modifying treatment is under hot debate. CD33 is one of the top-

ranked AD risk genes identified by genome-wide association studies. This review summarizes the recently advanced biology of CD33 and its association with AD. It also provides insights from a drug discovery perspective into the druggability, therapeutic strategies, and challenges to target CD33 for treating this devastating disorder.

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia among older adults and was first identified more than 100 years ago. It currently affects more than 46.8 million people worldwide [1]. Despite decades of substantial investment and intensive research, there is no disease-modifying treatment available for this devastating disorder. Neuropathologically, the AD brain is characterized by extracellular accumulation of amyloid plaques, which are composed of β -amyloid peptide ($A\beta$), and by intraneuronal accumulation of intracellular neurofibrillary tangles, which are composed primarily of aggregated forms of hyperphosphorylated tau protein [2]. In addition, it has long been recognized that neuroin-

flammatory changes are always present in AD brains and may play a causative role in AD etiology [3]. This is supported by recent converging evidence from genetic studies demonstrating a strong association between microglial pathways and the most prevalent form of late-onset AD (LOAD). Genome-wide association studies (GWAS) have linked 20 single nucleotide polymorphisms (SNPs) expressed by microglia with LOAD. These variants include APOE, TREM2, CD33, ABCA7, etc. [4, 5]. Whether these genes play a mechanistic role in the progression of AD remains unclear.

CD33 is one of top-ranked AD risk factors identified by GWAS and has been replicated in various genetic analyses, although it did not demonstrate a genome-wide significance in a large meta-analysis [6–14]. CD33 belongs to the sialic acid-binding immunoglobulin (Ig)-like family and is a myeloid cell receptor that is exclusively expressed by microglia and macrophages in the brain. rs3865444 and rs12459419 are the two main CD33 variants which may confer the risk for AD [6–17]. CD33 expression is elevated in AD patients' brains, where it is thought to modulate microglial activation and inhibit A β clearance [16–19]. The capability of microglia for clearance of A β seems to be regulated by CD33 surface expression and alternative splicing, likely through D2 domain-dependent activation [15–22]. As such, interventions through small molecules or immunotherapy may represent the main strategies for treating AD. This review summarizes the biology of CD33 polymorphisms and their association with AD. The review particularly provides insights from a drug discovery perspective into the possibility and challenges of targeting CD33 as a treatment for AD.

CD33 Structure and Ligand Binding

The CD33 gene maps on chromosome 19q13.33 in humans encoding a 67-kDa transmembrane glycoprotein [23]. In mammals, CD33 is expressed on hematopoietic and phagocytic cells, including hematopoietic progenitors, myelomonocytic precursors, macrophages, monocytes, dendritic cells, and microglial cells [23]. CD33 belongs to the sialic acid-binding Ig-like lectins (Siglecs) family [24]. Human CD33 binds preferentially to α -2,6-linked sialic acid at μ M to mM potency. The active site of CD33 contains a conserved arginine residue which is positively charged at physiological pH. Since sialic acids are typically terminal on glycoconjugates, the positively charged arginine forms salt bridges with the sialic acid of sugar residues, enabling a stable interaction [23–25].

CD33 is a type I transmembrane protein with its N-terminus in the extracellular space and the C-terminus in the cytosol [23–25] (Fig. 1). CD33 is a member of the Ig superfamily and thus has Ig domains and the structure of Ig fold. The CD33 gene comprises seven coding exons, which can be described from the extracellular to the cytosol as follows: exon 1 encodes an 18-amino-acid signaling peptide (SP, aa1–18) followed by a 31-amino-acid peptide and a premature stop codon. CD33 translation is initiated from an ATG within exon 1. A splice variant of CD33 retains intron 1, which leads to a frameshift such that the isoform encodes a prematurely truncated peptide including only the signal peptide (R1-CD33). The function of R1-CD33 is unknown. Exon 2 encodes the canonical Ig-like V-type (IgV) domain (aa19–135), which is the binding site of sialic acid-containing ligands and is considered as the functional domain of CD33. A splice variant short of exon 2 results in an inactive isoform (D2-CD33). Exons 3 and 4 encode a C2-type Ig repeat structural domain (C2-Ig domain, aa145–228). Siglec members differ by their numbers of C2-Ig domains. A few Siglec members contain multiple C2-Ig domains, allowing them to extend far from the cell surface and to bind trans-ligands (i.e., ligands found on other cells). CD33 contains only one C2-Ig domain and is the shortest Siglec family member [23]. This means that CD33 likely binds ligands (glycans or glycolipids) on the surface of the same cell (cis ligands or cis activation) and prevents CD33 from binding to other cells or foreign objects (trans ligands). Exon 5 encodes a transmembrane domain (aa260–282). Exons 6 and 7 encode two cytosolic immunotyrosine inhibitory motifs (ITIMs): a membrane-proximal ITIM (aa338–343) and a membrane-distal ITIM-like motif (aa356–361). The ITIM is the main domain for inhibitory signal transduction in cells; however, it lacks in mouse CD33, demonstrating its strong species variation. An ITIM-like motif is conserved between human and mouse and likely maintains the regulatory function related to endocytosis. The ITIM-like motif may also be involved in immunoreceptor tyrosine-based inhibitory signaling [23–25].

CD33 Function

The function of CD33 and its association with diseases have not been thoroughly elucidated. The function of CD33 is based on cell surface receptor-ligand interactions and cell types. Due to the exclusive expression of CD33 on immune cells, one important role of CD33 is its ability to modulate immune cell functions. In immune cells,

Fig. 1. Schematic depiction of CD33 exon structure and its inhibitory mechanism. The CD33 gene comprises 7 exons encoding 7 domains. From the extracellular to the cytosol, they can be described as domain 1 (D1) for a signal peptide (SP), D2 for an IgV ligand binding domain, D3–4 for an IgC domain, D5 for a transmembrane (TM) domain, D6 for an immunotyrosine inhibitory motif (ITIM), and D7 for a membrane-distal ITIM-like motif. In immune cells, cellular processes (such as phagocytosis, cytokine release, apoptosis, etc.) are coregulated by immunoreceptor tyrosine-based activation motifs (ITAM)-containing activating receptors and ITIM-containing inhibitory receptors. The inhibitory receptor CD33 can be constitutively activated by sialic acid-bearing glycoproteins and glycolipids, which are constantly constituted in amyloid plaques in the brains of Alzheimer's disease patients. When binding to ligands, the tyrosine within the ITIM of CD33 is phosphorylated and acts as a docking site for Src homology 2 domain-containing phosphatases (SHPs). This leads to dephosphorylation of cellular proteins, consequently downregulates activating signaling pathways initiated by phosphorylation (such as those induced by ITAMs), and ultimately results in inhibition of cellular function such as phagocytosis.

cellular processes (such as phagocytosis, cytokine release, apoptosis, etc.) are coregulated by immunoreceptor tyrosine-based activation motifs (ITAM)-containing activating receptors and ITIM-containing inhibitory receptors [25, 26]. When binding to its ligands, the tyrosine within the ITIM of inhibitory receptors is phosphorylated and acts as a docking site for Src homology (SH) 2 domain-containing proteins like SHP phosphatases. This leads to dephosphorylation of cellular proteins, which consequently downregulate activating signaling pathways involving phosphorylation, such as those induced by ITAMs [26]. CD33 is an inhibitory receptor. It can be constitutively activated by sialic acid-containing glycoproteins and glycolipids. The activated CD33 receptor recruits inhibitory proteins such as SHP phosphatases via its ITIM domains, resulting in an inhibition of cellular function such as phagocytosis (Fig. 1).

CD33 is also involved in several other processes [26, 27], such as adhesion processes in immune or malignant cells, inhibition of cytokine release by monocytes, im-

mune cell growth and survival through the inhibition of proliferation, and induction of apoptosis. Since mammalian cells are covered with sialic acid-containing glycans and glycolipids, binding to sialic acid residues of endogenous glycoproteins and glycolipids is thought to be one of the mechanisms by which immune cells recognize self from non-self via CD33 or other Siglec receptors [23, 26]. As such, Siglec receptors propagate the alleviated inhibitory signals when the immune cells encounter a non-self macromolecule.

CD33 in AD

CD33 and AD Susceptibility

Polymorphisms of CD33 have been implicated in modulating AD susceptibility and the pathology of LOAD [11–17]. rs3865444C is a common allele (>70%) and has been found to be associated with an increased risk of AD in European, Chinese, and North American populations

in four large-scale GWAS [6, 12–14]. This allele has also been tied to more severe cognitive decline in AD and lower MMSE scores [19]. In contrast, the minor A allele of rs3865444 (rs3865444A) confers protection against AD. The susceptibility and pathology of AD seems to be modulated by the expression of CD33 and the splicing of function-related isoform products [16–19]. Supportively, CD33 expression has been observed to be increased with the rs3865444C allele, but to be decreased with the protective rs3865444A allele [15–17].

In addition to modulating the expression of CD33, the rs3865444A allele is also associated with a robust increase in the proportion of alternative splicing of non-functional CD33, which is a CD33 isoform absent of ligand binding domain (often called D2-CD33 or CD33m). rs3865444 is located 373 bp upstream in the promoter region of the CD33 gene [15, 16]. It is therefore unlikely that rs3865444 directly affects splicing of exon 2 in CD33, and most likely the causal variant would be another SNP in exon 2. A mini gene assay has shown a close link of rs12459419 to CD33 exon 2 splicing. rs12459419 is located in exon 2 in a predicted binding site for the splicing factor SRSF2 and is in perfect linkage disequilibrium with the SNP rs3865444. The T allele of rs12459419 is co-inherited with the A allele of rs3865444 and increases the chance of exon 2 skipping, leading to a reduced expression of full-length CD33 and an increased expression of D2-CD33. One copy of rs12459419T decreases the production of full-length CD33 mRNA by 25.2% while two copies of rs12459419T decrease the production of full-length CD33 mRNA by 46.4% [22]. This dose-dependent reduction in CD33 functionality per copy of rs12459419T corresponds to a dose-dependent decrease in AD risk [15–17]. The relationship between genotype and gene expression appears to be consistent over the life course, suggesting that CD33 may be a marker of susceptibility.

CD33 and AD Pathologies

Senile amyloid plaques and neurofibrillary tangles are two major neuropathological markers of AD brain and are considered as major causes of cognitive disorders in AD [2]. Higher CD33 expression in the parietal lobe is associated with more advanced cognitive decline or disease status, but not tau pathology-associated Braak score [19, 21]. Other independent groups also found that carrying the rs3865444C risk allele appears to have no bearing on tangle formation. In contrast, those individuals have a higher probability of being positive for amyloid detector Pittsburgh compound B and a higher likelihood

of obtaining an AD diagnosis [21]. These findings suggest that CD33 may modulate amyloid-related pathophysiology rather than tauopathy in AD.

In the brain, CD33 is exclusively expressed by microglia and infiltrating macrophages [16, 17], hence the effects of CD33 on the microglia or macrophage network may be critical to the role of CD33 in AD. An emerging body of data identified multiple pathways that could explain the pathogenic nature of CD33 in AD. The increase in CD33 mRNA and protein levels was found to be coincidentally increased with the number of CD33-positive microglia in postmortem AD cortex [16, 17]. Studies using CD33^{−/−} mouse models indicated that knocking out CD33 results in lower A β levels and reduced amyloid plaque burden in the brain [17]. Since these mice do not exhibit altered amyloid precursor protein processing, this phenotype is likely associated with A β clearance. This supports the notion that reduced expression of CD33 allows more efficient phagocytic clearance of pathogenic A β by microglia and thus protects against AD. This finding was corroborated by another study using human monocytes and brain samples [21]. Other researchers further found that overexpression of ectopic CD33 in microglial line BV-2 cells reduces A β uptake [17].

It was further found that the IgV domain is essential for CD33's ability to suppress amyloid fragment uptake [28]. Studies in human brain cDNA indicated that rs12459419T is associated with an increased production of the atypical D2-CD33 lacking the IgV domain [22]. The atypical CD33 does not appear to inhibit A β phagocytosis based on the fact that expression of ectopic CD33, but not atypical D2-CD33, in BV-2 cells reduces A β uptake [17]. A similar assay performed by Bradshaw et al. [21] suggests that peripheral monocytes from individuals with the minor rs3865444 allele, which produce a high proportion of D2-CD33, exhibit enhanced A β phagocytosis compared to those from individuals who produce more full-length CD33. Hence, it is predicted that the increased full-length CD33 in AD brains may lead to an inhibited microglial phagocytosis of A β , resulting in impaired A β clearance and subsequent accumulation of A β in brains of AD patients and aging individuals. In contrast, a decrease in full-length CD33 or an increase in the proportion of D2-CD33 represents a decrease in normal CD33 function and enhanced A β clearance.

In addition to the mechanism that microglial cells are immunosuppressed by increased CD33 expression, the accumulation of A β in AD brains can also be explained by another possibility. Gangliosides and glycoproteins are major components on the surface of amyloid plaques

and are often with terminals of one or more sialic acids [29]. Amyloid plaques decorated by sialic acid-containing glycoproteins and glycolipids may activate CD33 signaling and then be masked against microglial recognition [30]. This results in hiding neuritic plaques, allowing them to evade immune surveillance, preventing the microglial clearing process and eventually leading to accumulation of amyloids [31]. It would be of interest to further investigate whether the interaction between gangliosides or glycan in amyloid plaque and CD33 (or any other Siglec, such as Siglec-11) on microglia plays a role in AD development.

Additionally, a recent study showed that the D2-CD33 isoform does not localize to cell surfaces; instead, it accumulates in peroxisomes. Cell stimulation and activation did not mobilize D2-CD33 to the surface. Thus, the D2-CD33 isoform may neither interact directly with amyloid plaques nor engage in cell surface signaling, demonstrating a loss of function mechanism [20]. Moreover, CD33 may interact with other microglial AD risk genes to influence AD onset and pathogenesis. These genes include TREM2 [32], DAP12/TYROBP [33], APOE, CD14, etc. [34]. Microglial phagocytosis seems to be a common phenotype linking CD33 to other innate immune gene risk alleles.

CD33 as a Therapeutic Target for AD: Possibilities and Strategies

Currently, A β - or tau-based therapies are major strategies for AD drug discovery, but have turned out to be a succession of failure in clinical trials [2]. Moreover, these therapies are likely to have only a partial effect on disease progression. Despite many challenges, targeting to genetically defined microglial-based genes such as CD33, TREM2, or APOE may enable a complement/augmentation because microglia-targeted therapies could not only remove toxic A β and tau through phagocytosis, but also have multiple effects on brains, such as the prevention of aberrant synaptic pruning via restoring microglial phenotypes to a healthier state.

CD33 is currently a highly-ranked LOAD risk gene, although its effect size is much smaller than that of APOE or TREM2. Since CD33 was identified from genetic association studies, it likely contributes to a certain extent to the disease etiology, either by actively participating in disease progression or by providing a more permissive environment. CD33 SNPs are genetic risk factors that are highly prevalent in the population (~40% minor allele

frequency) but confer a relatively small genetic risk [5–8]. The protective minor allele of CD33 has an odds ratio (the chance of developing the disease) of 0.89 (or 11% reduced risk) [5–8], hence it is concerned whether intervening in this pathway would be strong enough to have an effect, particularly if the intervention is after the onset of symptoms when the damage has already been initiated. However, it has been argued that a modest alteration resulting from CD33 SNP may only reduce AD risk modestly, whereas substantial modulation of CD33 signaling by a drug may have a larger effect. Additionally, the true effect of a susceptibility gene may be masked by compensation, including altered expression of a related gene family member. Therapeutic intervention may not allow time for compensation. Consequently, the therapeutic benefit may have a greater effect than that predicted by the genetic contribution. Because of the high selectivity within the Siglecs family, it is feasible to identify drugs specifically inhibiting CD33 activity. As a genetically defined therapeutic target, CD33 may also allow the selection of only those patients with the risk allele in the clinic which may increase the chances of observation of a positive therapeutic efficacy in clinical trials. These features may also be beneficial for CD33 being a drug target.

Since the protective allele of CD33 is associated with reduced CD33 expression and the alternative splicing producing a presumed inactive or dominant-negative form of the CD33 protein, it is relatively clear that the therapeutic approach for targeting CD33 would be inhibition of its activity via lowering levels of the total or active/functional form of protein. Since the sialic acid binding site of CD33 is required for CD33-mediated inhibition of A β phagocytosis [17], inhibition or blocking of the sialic acid binding site in CD33 has been inferred as an intervention strategy. GWAS and previous mechanistic studies have highlighted microglial phagocytosis in the context of AD. Thus, CD33-modulated microglial phagocytosis may be an important pathway for intervention.

Targeting CD33 through Small Molecules

Small molecular inhibitors are a traditional intervention and have been considered as viable CNS drugs. However, the druggability of CD33 by small molecules has not been proven because the region of CD33 that binds to its sialic acid ligand appears not to be a viable site. The sialic acid ligand binding region is very flat and does not contain any binding pockets. Additionally, this region is highly polar, and polar small binding molecules are unlikely to get into the brain [24, 25, 34]. As a result, target-

ing to CD33 should not be only restricted to the sialic acid binding domain and should also attempt to allosteric sites such as other regions in the V domain or regions between the C2 and V domains. In order to find a possible allosteric site, screening for both competitive inhibitors and allosteric modulators of CD33 should be pursued during CD33 inhibitor screening. Since drug targets need to be pharmacologically tractable for small molecule screening, resolving the currently unavailable 3D structure of CD33 binding domains will significantly facilitate candidate screening.

Targeting CD33 through Immunotherapy

CD33 antibodies may offer another means to target cell surface CD33 with high specificity and efficacy. It is conceivable that CD33 inhibitory antibodies could be used as a treatment for AD, especially when small molecules show unfavorable druggability. Notably, two CD33 antibodies, gemtuzumab ozogamicin (trade name Mylotarg) and lintuzumab, have been tested extensively in humans for treating acute myeloid leukemia (AML) and can effectively reduce cell surface CD33 expression in monocytes [35]. The humanized monoclonal antibody lintuzumab downregulated cell surface CD33 up to 50% in nondifferentiated U937 cells and up to 80% in PMA-differentiated U937 cells at a concentration as low as 10 ng/mL [22]. This concentration is about 0.1% of the plasma concentration of AML patients treated with lintuzumab [22]. Considering that antibody concentrations in the brain are about 0.1% of those in the plasma [7], peripheral infusion of lintuzumab at doses similar to those used in AML trials may be sufficient to impact CD33 in the brain. While the utility of lintuzumab in AD requires extended in vitro and in vivo analysis, its safety has been proven in clinical trials for AML [36]. These results, combined with its strong safety profile, support further evaluation of this antibody in AD research. In fact, a recent study has ranked lintuzumab as one of the top drug repurposing candidates for treating AD [37].

CD33 antibodies lower CD33 protein levels mostly by inducing internalization and degradation or by inhibiting CD33 activity. Since both gemtuzumab ozogamicin and lintuzumab are antibodies against the domain encoded by exon 2 [22], they will not recognize D2-CD33, which comprises 2–40% of total CD33 in the TCGA cohort. Individuals homozygous for the major allele of rs12459419 expressed 7.2% of their CD33 as D2-CD33; this portion increased to 17.4% in homozygous minor individuals [22]. Individuals carrying the minor allele of the SNP may be less responsive to treatment, in part because their cells

produce more of the D2-CD33 variant. These patients might be more responsive to a modified treatment using an antibody against a constitutively present CD33 epitope, e.g., the IgC2 recognizing HIM3–4 [35, 38]. Characterization of patients' rs12459419 genotype may be helpful in clinical studies and will be useful in determining optimal treatment. Obviously, CD33 immunotherapy should also not be restricted to targeting the sialic acid binding domain, but should potentially target allosteric sites.

Targeting CD33 through Other Approaches

Currently, the most parsimonious hypothesis for targeting CD33 in AD is that CD33 would need to be inhibited in the brain and therefore CD33-targeting drugs would need to cross the blood-brain barrier (BBB), which markedly restricts the druggability of CD33. It is a challenge for both CD33 small-molecule inhibitors and antibodies to penetrate the BBB. Recently, antisense oligonucleotides and viral delivery systems have been developed or considered as CNS drugs [39]. These modalities may expand the range of gene products that could be considered as druggable targets.

Furthermore, CD33 is expressed on all myeloid cells. While microglia are the likely culprits, it is unknown whether other cell types also confer or contribute to AD risk. Peripheral immune cells, such as monocytes, express most of the disease risk genes expressed by microglia. During the disease process, circulating monocytes infiltrate the brain and differentiate into macrophages, which superficially resemble, but are molecularly quite distinct from, microglia [40]. Infiltrating monocytes appear to play a beneficial role, possibly by removing amyloid plaques [40]. A recent study showed that an immune checkpoint blockade directed against the programmed death-1 protein – an important therapeutic target for stimulating the adaptive immune system to fight cancer cells – resulted in enhanced recruitment of monocytes into the brain, clearance of cerebral amyloid plaques, and improved cognitive performance in an A β -depositing mouse model [41], although a most recent study showed a negative result using several mouse models [42]. Due to the potential role of peripheral monocytes or macrophages in AD pathogenesis, it is reasonable to infer that peripheral immune cells or a combination of peripheral immune cells and microglia may also contribute to the role of CD33 in AD. The implication of this concept for treatment is that the therapeutic agent may not need to get into the brain, which considerably lowers the hurdle of CNS drug discovery.

Challenges and Perspective

Similar to other disease risk genes, there are many caveats that need to be considered before pursuing CD33 as a drug target. First of all, it should be further investigated whether the CD33 risk allele is a disease-causing mutation or just a linkage disequilibrium with the polymorphism that is truly responsible for the disease. Secondly, it is uncertain whether we can manipulate the function or levels of the target therapeutically. This may be particularly challenging for CD33 since the odds ratio to AD is not dramatically robust. Additionally, the risk alleles identified by GWAS are present at conception, but therapeutic intervention in AD is likely to begin decades later, after onset of symptoms or appearance of diagnostic biomarkers. It might be a tall order manipulating these genes to reverse damage that has been potentially accumulating over a lifetime.

As described earlier, CD33's unproven structural druggability impedes a small-molecule approach. CD33 inhibitory antibodies also face a number of challenges. In addition to low BBB penetration, the antibody approach may suffer from target-mediated disposition. Different from A β and tau antibodies, the majority of antigens for CD33 antibodies are in the periphery. This would cause a "sink" effect, and it would be even harder to achieve sufficient concentrations in the brain. Moreover, peripherally administered antibodies could completely saturate CD33 in the blood, resulting in safety consequences. Although CD33 knockout mice have very mild phenotypes and inhibiting peripheral CD33 may be viable from a safety perspective [36], massive decoration of monocytes with a CD33 antibody may have additional consequences that were not predicted by the knockout mice, such as antibody-dependent cell killing of monocytes via complement-dependent cytotoxicity and/or antibody-dependent cell-mediated cytotoxicity. Antibodies can be engineered to eliminate the potential antibody-dependent cell killing, e.g., using IgG4 isotype to eliminate or limit binding to Fc receptors or removing Fc-mediated effects through methods such as mutating the binding site for Fc receptors [28]. Particularly, an approach that can shuttle CD33 antibody across the BBB may provide a solution to both brain penetration and the potential toxic cross-reactivity in the periphery; however, this method has not been shown to be a success in clinic studies [34]. Since CD33 has a strong species specificity, while work with human in vitro systems to study biology and intervention is feasible, humanized CD33 mice will be a necessary tool for target engagement confirmation, in vivo preclinical proof

of concept studies, and pharmacokinetics and toxicology evaluation. Moreover, due to natural turnover of CD33 in blood cells, pharmacokinetic/pharmacodynamic modeling and dosing considerations must be taken into account. Furthermore, a more in-depth genetic screening is also important to uncover functional variants that shed light on these mechanisms and/or location in specific functional domains, alternative splice sites, or regulatory regions. As recent evidence implicates that microglia play an important role in tau clearance and propagation [19], it might be worthwhile to systematically investigate whether microglial receptor CD33 plays a role in tau pathogenesis, even though previous limited data did not indicate a strong direct association.

Summary and Conclusions

Given the genetic link between CD33 and LOAD, the exclusive expression of CD33 in microglia, and the important role of microglia in AD etiology, it is logical to consider potential therapeutic attempts to regulate disease status through modulation of CD33 expression and its function in microglia. Small-molecule and CD33 immunotherapy targeting the CD33 activation sites are likely two major avenues of intervention, although challenges exist on BBB penetration and possible mechanism-based toxicity. Further in-depth studies are warranted to understand the extent and consequences of CD33 involvement in order to pursue therapeutic strategies with optimal efficacy, but minimal unwanted modulation of immune cell phenotypes.

Disclosure Statement

The author declares no competing interests.

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