Translating CD33 genetics to an Alzheimer's disease pharmacologic agent

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Genome-wide association studies identified the single nucleotide polymorphism (SNP) rs3865444, located near CD33, as a modulator of Alzheimer's Disease (AD) risk. CD33 is a sialic-acid binding inhibitory receptor expressed by microglia in the brain and immature monocytes in the periphery.

CD33 has been shown to have an immunosuppressive when activated by ligand binding. To elucidate the SNP actions, we identified CD33 isoforms expressed in human brain as a function of genotype. We found a significant association between rs3865444 genotype and inclusion of exon 2 in mature CD33 mRNA. This association showed a robust allelic dose dependence; compared to individuals that are major allele homozygotes, the minor allele homozygotes had a 45% reduction in mRNA encoding typical CD33 and a 0.82 AD odds ratio. Studies with transfected cells in vitro demonstrated that rs12459419, an exon 2 SNP that is perfect co-inherited with rs3865444, directly modulates the efficiency of exon 2 splicing. Since exon 2 encodes the sialic acid binding domain of CD33, we interpret this finding overall as suggesting that a more robust CD33 inhibitor may reduce AD risk further, within an overall model wherein CD33 inhibition enables microglial activation.

Considering possible inhibitors, we noted that antibodies such as Lintuzumab which target CD33 are safe but ineffective when tested in human acute myeloid leukemia trials. We found that Lintuzumab is highly effective and potent in downregulating CD33 from the cell surface in vitro. Overall, since the mechanisms underlying AD genetics have been shown by nature to alter AD risk, pharmacologic agents that magnify these genetic effects may prove to be robust agents for reducing AD risk.