The Role of CD33 in Microglial Neuroinflammation and Phagocytosis

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Alzheimer's disease (AD) is the leading cause of dementia worldwide, where patients often experience memory loss and the inability to perform daily tasks.[1] β-amyloid (Aβ) aggregation, tau-proteins tangles, and neuroinflammation are the main features of AD. Microglia are the primary immune cells in the brain that remove the extra accumulation of Aβ or tau-proteins via phagocytosis.[2] Genetic studies indicate that risk genes for AD are highly expressed in microglia. Further evidence shows that patients with AD have higher expression of CD33, a microglial transmembrane receptor.[3] However, the functions of those risk genes are largely unknown during AD development.

In this study, we plan to manipulate CD33 expression in microglia and examine microglial functions with different CD33 expression levels. We will first check the CD33 expression patterns during microglial pro-inflammatory (M1) or anti-inflammatory (M2) activation. For this purpose, we will stimulate a human microglial cell line (HMC3) with lipopolysaccharide (LPS) into the M1 phenotype and with interleukin (IL)-4 into the M2 phenotype. Gene expression of CD33 along other well-known M1/M2 genes will be quantified by real-time-polymerase chain reaction (RT-PCR). The phagocytic capacities under each activation will also be measured with fibril Aβ phagocytosis. Next, we will use the CRISPR-Cas9 system to knock out CD33 gene expression in HMC3 and study the phagocytic capacities of the transduced cells. Preliminary data suggests that higher CD33 expression is a consistent phenotype seen in AD patients. Along with using HMC3, we will study the functions of CD33 in a microglia-like cellular model (iMGLCs) induced from human peripheral blood monocytes. Studying the role of CD33 in AD development will facilitate novel therapeutic targets for AD treatment.

Key Words: Alzheimer's disease, β-amyloid, pro-inflammatory, CD33, phagocytosis