ALZHEIMER DISEASE

Functional dissection of *CD33* locus implicates innate immune response in Alzheimer disease pathology

In a new study, researchers have shown that the *CD33* locus—a recently identified susceptibility locus for Alzheimer disease (AD)—is linked to altered monocyte function, suggesting a role for these innate immune cells in AD pathology.

CD33 is expressed on innate immune cells—namely myeloid progenitor cells, mature monocytes, and macrophages—and a risk allele at this locus, *rs3865444^C*, has recently been linked to AD susceptibility. In the new study, led by Philip De Jager, lead author Elizabeth Bradshaw and colleagues hypothesized that, given its known expression pattern, the *CD33* locus could influence the function of monocytes.

First, genotype analysis in a sample of 32 young cognitively normal individuals revealed a sevenfold increase in *CD33* expression on monocytes in individuals carrying the *rs3865444^{CC}* risk genotype versus those with a protective genotype. “We found that the influence of the risk allele on

Section of the cortex from a patient with Alzheimer disease showing neuritic amyloid plaques (red) and *CD33*⁺ cells (brown). Image courtesy of J. Schneider.

protein expression is present even in young adults, suggesting that aspects of AD pathology may start early in the life course,” says Bradshaw. A replication study in 175 older patients either with or without AD also showed a positive association between *CD33* expression on monocytes and presence of *rs3865444^C*.

Next, Bradshaw *et al.* found that monocytes expressing *rs3865444^C* had a

reduced ability to phagocytose amyloid- β . Presence of the risk allele was associated with greater burden of fibrillar amyloid in older asymptomatic individuals who were profiled using Pittsburgh compound B imaging, and with neuritic amyloid plaques in the brains of older individuals at autopsy.

Examination of tissue sections from brains of older patients with AD revealed that *CD33*-expressing cells had morphological characteristics of microglia and macrophages, and these cells were found near neuritic plaques, consistent with another recent study.

“If the role of peripheral immune cells such as monocytes is validated in AD, it could provide an attractive target for immunomodulating therapies,” says De Jager.

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