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NEUROLOGIC DISORDERS NEWS ARTICLE

Reprogramming microglial functional state has therapeutic potential for AD

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By John Fox, Staff Writer

Modulating the functional state of microglia by injecting **IL-33** to reprogram their epigenetic and transcriptomic profile may represent a new therapeutic strategy for Alzheimer's disease (AD), Hong Kong University of Science and Technology (HKUST) scientists reported in the April 21, 2020, edition of *Cell Reports*.

"While we have previously shown that modulating the central nervous system (CNS) cytokine milieu, for example by IL-33 injection, can regulate microglial functions and ameliorate AD pathology in transgenic mouse models, the underlying mechanism was unclear," said study leader Nancy Ip, Morningside Professor of Life Sciences at HKUST.

"This study has shown that the functional state transition of microglia induced by IL-33 injection is important for their clearance of misfolded beta-amyloid (Abeta) peptide [accumulation of which characterizes AD], so targeting the transcriptomic state transition of microglia may offer a new therapeutic strategy for AD," said Ip.

As the major immune cell type in the CNS, microglia maintain brain homeostasis through immune surveillance and neurotrophic support. However, disturbed CNS homeostasis due to accumulation of waste products activates the microglia to adopt an activated phenotype, in order to restrain cytotoxicity and limit nearby cell damage.

Upon aging, genetic risk factors, inflammation, and accumulation of aging-related factors in the CNS impair microglial functions and contribute to the neurodegeneration seen in AD.

In AD, the accumulation of extracellular misfolded Abeta protein deposits triggers microglial activation, leading to its migration toward Abeta plaques and initiating phagocytosis.

However, as AD progresses, microglia become dysfunctional, resulting in impaired clearance of misfolded Abeta peptide and inefficient barrier formation around Abeta plaque.

These both further exacerbate Abeta plaque accumulation, together with synaptic impairment and neuronal death in AD. Interestingly, enhancing microglial Abeta clearance activity by modulating CNS cytokines, such as replenishing IL-33 or inhibiting IL-10, IL-12/IL-23 or NLRP3 inflammasomes, has been shown to reduce Abeta pathology and improve cognitive performance in AD transgenic mouse models.

Moreover, single-cell RNA-sequencing (scRNA-seq) analysis in AD mouse models has demonstrated that homeostatic microglia gradually transform into disease-associated microglia (DAM).

Transcriptome profiling has revealed that this microglial subpopulation highly expresses genes that are key regulators of phagocytic processes.

The DAM breaks

While it is unclear how the DAM state's transcriptome drives microglial functional impairment, manipulating microglial functions through reprogramming its transcriptome may be a potential therapeutic strategy against AD.

Notably, both IL-33 injection and NLRP3 inflammasome inhibition, which have demonstrably beneficial outcomes in AD mouse models, regulate the transcriptomic signature of microglia.

However, the molecular pathways that reprogram the dysregulated microglial phenotype in AD, resulting in beneficial outcome, remain unclear.

In their new *Cell Reports* study, Ip and her team at HKUST demonstrated that injecting IL-33 into an Abeta-deposition transgenic mouse model ameliorated Abeta pathology.

"We used immunohistochemical staining to show that a single IL-33 injection could reduce the Abeta load in the cortical brain regions of AD transgenic mice by 30-40% within 2 days," Ip told *BioWorld Science*.

She and her team then demonstrated that this was achieved by reprogramming microglial epigenetic and transcriptomic profiles, in order to induce a microglial subpopulation with enhanced phagocytic activity.

These IL-33-responsive microglia (IL-33RMs) were shown to express a distinct transcriptomic signature, in particular by increased major histocompatibility complex class II (MHC II) genes and homeostatic signature genes.

"The transcriptome signature of IL-33RMs was identified by single-cell transcriptomic analysis of microglia from IL-33-treated and control APP/PS1 mouse models of Abeta pathology," said Ip.

"Interestingly, we found that the transcriptome profiles of IL-33RMs were enriched with MHC-II genes, which are crucial for antigen presentation and resemble early stage DAM.

"While the induction of DAM in early stage AD has been proposed to benefit disease pathology, there is lack of experimental evidence. Together with the functional characterization of IL-33RMs, our data suggest that inducing early stage DAM may result in beneficial outcomes in AD."

IL-33 remodels chromatin accessibility and PU.1 transcription factor binding at the signature genes of IL-33RM were shown to modulate their transcriptome reprogramming.

"These findings show that the IL-33-induced microglial state transition is controlled by remodeling of the chromatin accessibility and PU.1 binding landscape," noted Ip. "Importantly, this suggests that targeting chromatin remodeling proteins or PU.1 could potentially stimulate microglial state transition similar to that induced by IL-33."

In particular, disrupting the PU.1-DNA interaction using a small-molecule inhibitor of PU.1 was shown to abolish the IL-33-induced microglial state transition and Abeta clearance, revealing an essential role of PU.1 in regulating microglial state transition during the cytokine-induced activation.

Together, these findings demonstrate that IL-33-induces remodeling of the epigenetic and transcriptional profiles of microglia and drives the functional state transition, which alleviates the AD pathology.

"This suggests that modulating microglial functional state in AD represents a promising new therapeutic approach in AD," she said.

"We have shown that the microglial state transition is regulated by multiple levels of control, including cytokine signaling cascade, the epigenetic landscape and the transcriptomic profile, broadening the range of therapeutic targets." (Lau, S.F. et al. Cell Rep 2020, 31(3): 107530).

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