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MOTOR NEURON DISEASE

Proinflammatory monocytes might contribute to ALS progression

Peripheral monocytes have a proinflammatory gene expression profile in patients with amyotrophic lateral sclerosis (ALS), a new study has found. This proinflammatory state might have a role in disease progression, and could offer new clinical opportunities.

Previous work has shown that microglia are activated in the CNS of patients with ALS, and that T cell function is systemically altered, but the role of the innate immune system in the periphery has not been determined. In their new work, Stanley Appel and colleagues aimed to address the question of whether monocytes contribute to pathology.

"Evidence of immune alterations in humans and mice led us to characterize the gene expression phenotype of ALS monocytes," explains Appel. "The goal was to use an unbiased approach to determine whether peripheral circulating innate immune cells exhibited a proinflammatory phenotype."

> "monocytes … may contribute to accelerated clinical demise in ALS"

The researchers isolated monocytes from 43 patients with ALS and 22 healthy controls using a negative selection procedure that ensured gene expression was not altered. Deep RNA sequencing of monocytes from approximately half of the participants identified 233 genes that were differentially expressed in monocytes from patients with ALS compared with those from healthy controls. Nine of the top 10 differentially expressed genes are involved in the proinflammatory responses of monocytes. Measurement of mRNA levels in monocytes from all participants confirmed the proinflammatory gene expression profile of monocytes from patients with ALS.

The team also compared the gene expression profiles of monocytes from patients who had rapidly progressing ALS with those from patients who had slowly progressing ALS, and found that rapid disease progression was associated with a higher number of differentially expressed, immune-related genes in monocytes. "These data suggest that the increased proinflammatory gene expression in monocytes isolated from patients with rapidly progressing ALS may contribute to accelerated clinical decline in ALS," says Appel. "The findings also indicate systemic involvement of activated monocytes in addition to T cells in the pathophysiology of ALS."

Appel also comments that the proinflammatory gene expression profiles of monocytes in ALS and their association with the rate of disease progression has several potential clinical applications. "Proinflammatory monocytes could serve as a meaningful biomarker of disease progression, and the reduction of proinflammatory monocyte markers provides a potential opportunity to slow ALS disease progression," Appel concludes.

Ian Fyfe

ORIGINAL ARTICLES Zhao, W. *et al.* Characterization of gene expression phenotype in amyotrophic lateral sclerosis. *JAMA Neurol.* http://dx.doi.org/10.1001/jamaneurol.2017.0357 (2017)