Nature Reviews Neurology | Published online 17 Nov 2017; doi:10.1038/nrneurol.2017.164

> blood-derived human Aβ can enter the brain and cause AD-type neuropathology and neuronal dysfunction

ALZHEIMER DISEASE

Blood-derived Aβ induces AD pathology

Alzheimer disease (AD) neuropathology is characterized by deposits of amyloid-β (Aβ) protein in the brain, which are thought to originate within the brain itself. Many other peripheral tissues also produce Aβ, but the role of peripheral Aβ in AD pathology is unclear. Now, a study in *Molecular Psychiatry* shows that blood-derived Aβ can induce AD-type pathology.

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"Aβ is also produced in peripheral tissues or cells, such as platelets, skin fibroblasts, skeletal muscles and osteoblasts, and secreted into blood circulation," comment corresponding authors Yan-Jiang Wang and Weihong Song. "Previous studies suggest that systemic diseases, such as systemic chronic inflammation and dysfunctions of liver and kidney, are associated with higher blood Aβ levels or AD risk, which prompted us to conduct this study."

After first demonstrating that blood-derived human Aβ can enter the brains of wild-type mice, the authors used a model of parabiosis between human Aβ-expressing AD mice harbouring a mutant β-amyloid precursor (APP) transgene and their wild-type littermates. "The reason we decided to adopt this approach is that this model allowed the wild-type mice to continuously receive the human Aβ from parabiotic APP transgenic mice via the blood in a shared circulation system," explains Wang.

Notably, parabiosis with APP transgenic mice led to an accumulation of human Aβ and the formation of cerebral β-amyloidosis in the brains of wild-type mice. In addition, blood-derived Aβ could induce tau hyperphosphorylation in the brains of wild-type mice and was associated with neurodegeneration, neuroinflammation and cerebral microhaemorrhage. Finally, wild-type mice showed neuronal dysfunction after parabiosis with APP transgenic mice. Together, these data suggest that blood-derived human Aβ can enter the brain and cause AD-type neuropathology andneuronal dysfunction.

"We plan to investigate the systemic mechanism underlying the pathogenesis of AD, such as the impact of dysfunction of peripheral tissues and organs on the development of AD, and to find relevant diagnostic biomarkers and develop therapies from the systemic approach. The implications for future research are that the brain works with the rest of the body and we should consider the whole of the body when we work to understand and tackle the disease," concludes Wang.

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ORIGINAL ARTICLE Bu, X. L. *et al.* Blood-derived amyloid-β protein induces Alzheimer's disease pathologies. *Mol. Psychiatry* http://dx.doi.org/10.1038/mp.2017.204 (2017)